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PEDIATRICS BOARD REVIEW

CORE CURRICULUM

BOOK 4

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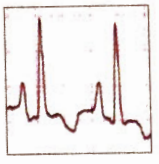

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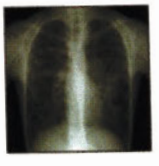

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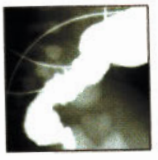

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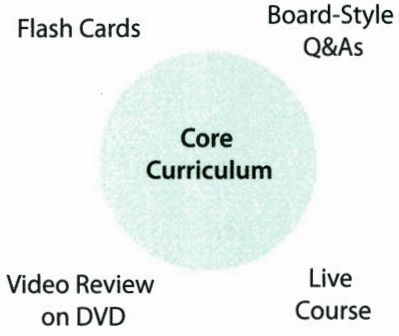

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Burgundy type applied to selected terms and phrases gives a tonal emphasis to the text, much the way a teacher would use inflection in a great lecture. This also alerts you to key facts and fine points of distinction.

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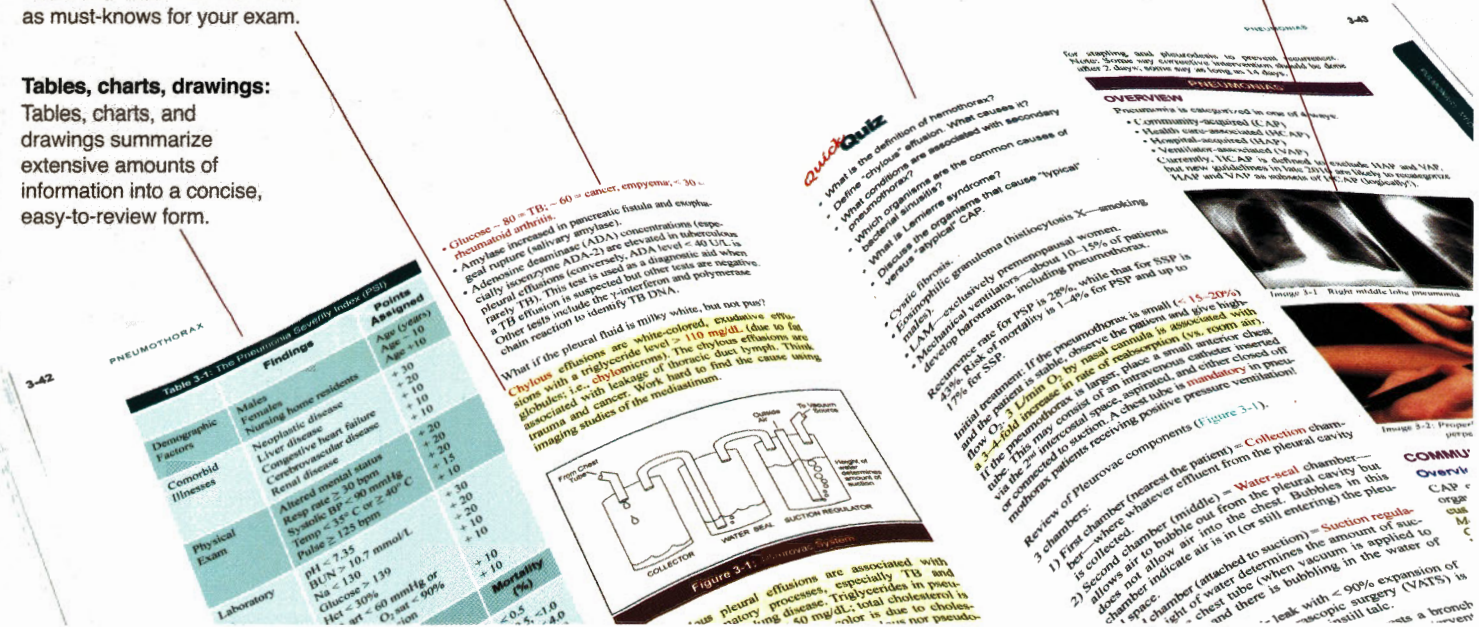

MedStudy®

PEDIATRICS BOARD REVIEW

CORE CURRICULUM

5th EDITION

Book 4 of 5

Topics in this volume:

Cardiology

Respiratory Disorders

Gastroenterology & Nutrition

Authored by J. Thomas Cross, Jr., MD, MPH, FAAP with Robert A. Hannaman, MD

NOTICE: Medicine and accepted standards of care are constantly changing. We at MedStudy do our best to review and include in this publication accurate discussions of the standards of care and methods of diagnosis. However, the author, the advisors, the editors, the publisher, and all other parties involved with the preparation and publication of this work do not guarantee that the information contained herein is in every respect accurate or complete. We recommend that you confirm the material with current sources of medical knowledge whenever considering presentations or treating patients.

A NOTE ON EDITORIAL STYLE: There is an ongoing debate in medical publishing about whether to use the possessive form that adds "'s" to the names of diseases and disorders, such as Lou Gehrig's disease, Klinefelter's syndrome, and others. We acknowledge there is not a unanimous consensus on this style convention, but we think it is important to be consistent in what style we choose. For this publication, we have dropped the possessive form. The *AMA Manual of Style*, *JAMA*, *Scientific Style and Format* and *Pediatrics* magazine are among the publications now using the non-possessive form. MedStudy will use the non-possessive form in this Core Curriculum when the proper name is followed by a common noun. So you will see phrasing such as "This patient would warrant workup for Crohn disease." Possessive form will be used, however, when an entity is referred to solely by its proper name without a following common noun. An example of this would be "The symptoms are classic for Crohn's."

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PEDIATRICS BOARD REVIEW

PEDS

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Authored by J. Thomas Cross, Jr., MD, MPH, FAAP
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CARDIOLOGY

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Cardiology

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PHYSICAL EXAMINATION

OVERVIEW

The physical examination (and history!) can provide as many clues as any diagnostic test for the diagnosis of cardiovascular disease. (Well, isn't that what every cardiologist told you during medical school and residency?) The ABP knows this too; so expect the Boards to give you more history and physical examination clues than "echo" results!

SKIN

Look at the color of the skin and mucous membranes. Cyanosis refers to a dusky blue color that occurs due to an excessive amount of reduced hemoglobin (unoxygenated) in the circulation system. Most commonly, you will see this color in the lips, mucous membranes, and nail beds. Usually, it can be seen quite readily if the arterial oxygen saturation is < 85%, but it may be difficult to see with higher oxygen saturation of 88–92%.

Peripheral cyanosis may also occur with normal oxygen saturation and is due to reduced peripheral circulation, which allows the tissues to extract more oxygen, leaving the venous end of the capillaries with more reduced hemoglobin. In this situation, the extremities may be cold and blue, while the mucous membranes and tongue are pink. In infants and children, peripheral cyanosis occurs most often with exposure to cold, with polycythemia, and sometimes even in normal newborns and young infants (acrocyanosis, a benign condition). Central cyanosis is due to arterial desaturation and is best seen in the tongue, oral mucous membranes, and trunk. Cyanosis of just the lower extremities and toes, and not the fingers (differential cyanosis), could indicate aortic arch obstruction or persisting pulmonary hypertension with ductal right-to-left shunting of desaturated blood. Cyanosis of the preductal structures (e.g., fingers), but not the postductal structures (e.g., toes), is termed reverse differential cyanosis. This indicates transposition of the great vessels, with right-to-left shunting of saturated blood through the ductus.

Petechiae can indicate infective endocarditis, but this can also be indicative of other things and, thus, is rather nonspecific. Splinter hemorrhages of the nail beds are more indicative of endocarditis.

Other skin findings, such as café-au-lait (neurofibromatosis) or ash leaf spots (tuberous sclerosis), may indicate disorders associated with heart defects.

ARTERIAL PULSES

Abnormalities of arterial pulses can indicate significant cardiac anomalies. Significant delay or absence of the femoral pulse, compared to the radial pulse, indicates coarctation of the aorta. Pulse quality can also be a helpful indicator: You see rapid rising or bounding pulses with large patent ductus arteriosus (PDA) or aortic valve insufficiency; slow-rising pulse can indicate aortic stenosis or hypertension.

VENOUS PULSES

You can observe venous pulses in the neck, and the mean jugular venous pressure gives a good measure of mean right atrial pressure. Healthy pediatric patients may have minor jugular venous distension and faint pulsation. Neck veins are not commonly seen in infants. Prominent jugular veins reflect obstruction, worsened ventricular filling due to poor compliance, or abnormal back flow.

The *a* wave is a venous wave that occurs just before the first heart sound and is due to atrial contraction. A large *a* wave usually indicates elevated right ventricular, end-diastolic pressures. Think about it … if the right atrium contracts while there is higher filling pressure in the right ventricle, the blood is going to be pushed back into the neck—and you'll see it. "Cannon" *a* waves occur when the right atrium contracts against a closed tricuspid valve—which can occur with AV dissociation (3rd degree heart block or junctional rhythm) or ventricular tachycardia.

The *v* wave is due to increasing volume filling and to concomitant, increasing pressure in the right atrium. It begins late in ventricular systole and in diastole; it is large with poor ventricular compliance and in severe tricuspid regurgitation.

AUSCULTATION OF THE HEART

First Heart Sound (S_1)

You can best hear the first heart sound (closure of the atrioventricular valves—tricuspid and mitral valves) at the apex or lower left sternal border. It is usually single or narrowly split. First heart sounds are never heard better at the base than at the apex. The loudness will vary, depending on the force of atrioventricular valve closure. It is loud in mitral stenosis, increased ventricular contractility, or a short PR interval—as the valves come together forcefully at the beginning of systole. By contrast, with decreased contractility, the first heart sound is soft, as is seen in myocarditis.

Clicks are heard near the first heart sound. Ejection clicks with pulmonary valve stenosis occur early in systole at the left base of the heart and may vary with respiration. You generally hear aortic ejection clicks at the apex. Aortic clicks do not vary with respiration. Palpation of the pulse can be helpful to differentiate from first heart sounds, which precede the pulse, and clicks that are usually simultaneous with the pulse. You can hear systolic ejection clicks when there is an enlarged great vessel at the base of the heart or when there is a thickened/abnormal semilunar valve. Examples of these are:

- Thickened semilunar valves (e.g., aortic stenosis, bicuspid aortic valve, truncus arterious [multi-valved great vessel], pulmonic stenosis)

- Enlarged aorta (e.g., tetralogy of Fallot)
- Truncus arteriosus

Nonejection clicks occur later in systole and are heard at the left lower sternal border or the apex. For example, a midsystolic click at the apex suggests mitral valve prolapse.

Second Heart Sound (S_2)

The second heart sound reflects closure of the aortic valve, then the pulmonic valve. Normally, the second heart sound (S_2) will have "physiologic" splitting, which results from increased venous return with inspiration. What happens is that, when you inspire deeply, you increase right ventricular volume, which, in turn, causes delayed right ventricular emptying, which then causes delayed closure of the pulmonic valve. Thus, you get a widening between the aortic and pulmonic valve closure and a splitting of the second heart sound shortly after inspiration. It is difficult (but not impossible) to discern splitting in infants because of their rapid heart and respiratory rates. Therefore, if such splitting is easily heard in an infant, suspect a large left-to-right atrial shunt (ASD) or venous shunt (anomalous pulmonary venous return).

In transposition of the great vessels, the aortic valve is anterior and directly under your stethoscope—so aortic closure is very loud and best heard at the upper left sternal border. In tetralogy of Fallot, the aorta is wide and dextroposed, and the pulmonary artery is located anterior and is smaller than usual; this results in a single, second heart sound that is heard loudest at the lower left sternal border.

Wide splitting (persistent) is due to delayed right ventricular emptying and can indicate possible atrial septal defect (ASD), right bundle-branch block (RBBB), or pulmonic stenosis. Paradoxically, split S_2 (splitting during expiration rather than inspiration) is due to a delay in left ventricular emptying, with the aortic closure sound coming after the pulmonic. You hear this in severe aortic stenosis or with LBBB.

Third Heart Sound (S_3)

You can hear the third heart sound in early diastole, when there is rapid, passive filling of a "relatively stiff" ventricle. It can be normal in children and pregnant women. Pathologic conditions that cause an S_3 can include left or right ventricular dysfunction or stiffness and AV valve regurgitation.

Fourth Heart Sound (S_4)

The fourth heart sound occurs in late diastole, when atrial contraction fills the ventricle. It is almost always abnormal. It can be heard with aortic stenosis, mitral regurgitation, hypertrophic cardiomyopathy, and hypertension with left ventricular hypertrophy.

"INNOCENT" MURMURS

Overview

These are murmurs that are due to normal slow turbulence and vibration, and they do not indicate pathology. In infancy, the most common murmur is physiologic peripheral pulmonic stenosis (PPPS) and, occasionally, a Still's murmur; but after age 2, many children will have at least one of the murmurs described below.

Systolic Innocent Murmurs

All of these murmurs are short and soft (grade III/VI or less). They get louder when the child is placed supine, because stroke volume increases with this maneuver. They also get louder with exercise, anxiety, anemia, or fever. They may get softer or disappear with a Valsalva maneuver (if Valsalva increases the murmur, think hypertrophic cardiomyopathy or obstructive left heart lesions!).

Still's Murmur

This is a systolic ejection murmur with a musical quality or vibratory character that some describe as similar to a plucked-string instrument or kazoo. You can hear it best in the lower precordium, not in the back. It decreases in intensity with expiration and positional changes that decrease venous return (e.g., standing). The musical quality is what makes this easily recognizable. It is very common in childhood!

Basal Ejection Systolic Murmur

You hear this murmur at the base, and it is mid-pitched and ejection in character. It does not have musical components. It can be difficult to distinguish from mild pulmonic or aortic stenosis. Stenosis usually is harsher and longer, and there may be a systolic ejection click if there is an associated bicuspid aortic valve (especially on the Boards).

Supraclavicular Arterial Bruit

The bruit is due to turbulence in the subclavian and carotid arteries, which, in turn, is due to increased acceleration in early systole. It is very short and early, and it ends before the 1st third of systole. It is easy to diagnose by its shortness and supraclavicular location.

Physiologic Peripheral Pulmonic Stenosis (PPPS)

PPPS is due to fetal anatomy. For several weeks after birth, the right and left pulmonary arteries are much smaller than, and come off at a right angle to, the large main pulmonary artery. This causes turbulence and results in a soft, harsh systolic ejection murmur best heard in the axillae and both the right and left hemithoraces. By 12 months of age, the branch pulmonary arteries become larger, and the angle at which they come off opens up; thus, the murmur usually disappears during this time period.

QuickQuiz

- Differentiate peripheral from central cyanosis.
- What does significant delay, or absence of, the femoral pulse compared to the radial pulse indicate?
- What does a rapid rising or bounding pulse indicate?
- What may a systolic ejection click indicate?
- In what conditions do you hear wide splitting of the second heart sound?
- Which is abnormal in a child: a third or fourth heart sound?
- What is the most common "innocent" murmur in an infant?
- What happens when you place the child in a supine position? What will Valsalva maneuvers do to most "innocent" murmurs?
- What distinguishes Still's murmur from others?
- Where on the thorax would you usually hear PPPS?
- What causes a venous hum murmur?

Continuous Innocent Murmurs

Venous Hum

Venous hum is due to blood draining down the collapsed jugular veins into the dilated intrathoracic veins. The high velocity makes the vein walls "flutter," resulting in a low-pitched murmur. It is usually absent when the patient is supine, because the neck veins are distended and there is no pressure gradient between the two areas. Valsalva maneuver, turning of the head, or compression of the jugular vein will also make the murmur go away. Venous hum is very common in childhood.

THE 15-LEAD ECG

Refer to Figure 12-1 as we go over the basics of ECGs. Note: If you don't have a lot of time, just skip to the "yellow highlighted" areas.

A lead tracing is positive if the wave of depolarization spreads toward the positive pole of that lead, and a tracing is negative if it spreads away. The tracing is isoelectric (equal forces above and below) if the wave spreads at a 90° angle to it. For instance, if II is isoelectric, look for the maximum projection to be at –30 or +150 degrees (i.e., 90 degrees to the left or right of II).

With the 15-lead ECG, the wave of depolarization is recorded on both the frontal and horizontal planes, giving a

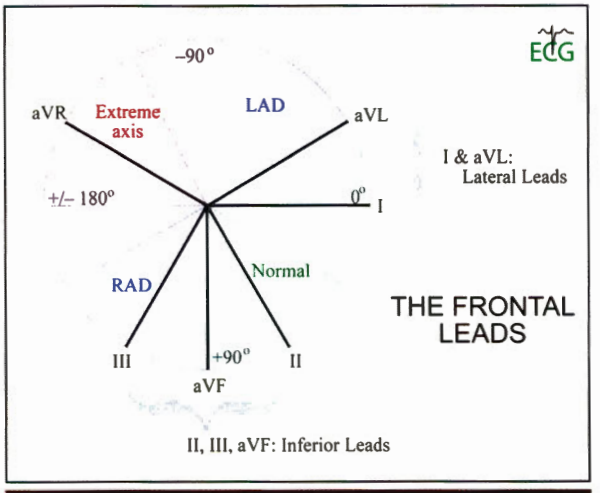

Figure 12-1: Axis Determination Diagram

3-dimensional representation of the heart. The projection of the electrical activity of the heart onto the frontal plane is recorded by the frontal leads I, II, III, aVR, aVL, and aVF. On the horizontal plane, it is recorded via electrodes placed in the V1–V6 position. In pediatrics, an additional V7 is added, as well as right chest leads to include V4R, V3R—placed the same as V3 and V4, except on the right side of the chest. These additional leads in children give you a better look at the left ventricle (V7) or a better look at the right ventricle (V3R, V4R). Depolarization moving toward the lead causes a positive deflection (P wave and QRS), as does repolarization moving away from the lead (T wave).

The frontal leads give inferior-superior, left-right information.

The horizontal leads relay anterior-posterior-lateral information. Think of V1 as looking at the right side of the heart while V6 looks at the left side. The QRS in V1 is positive when the right ventricle (RV) is depolarizing (and negative when the LV is depolarizing), whereas the QRS in V6 is positive when the LV is depolarizing (and negative when the RV is depolarizing). Because of right ventricular dominance at birth, the R in V1 is larger than the S in V1, and, with age, the R wave in V1 decreases (and increases in V6).

AXIS DEVIATIONS

At birth, the infant has a relatively thick right ventricle; the mean QRS axis points anteriorly and to the right, giving RAD (70° to 180°) and large R waves in the right precordium. The QRS axis in the frontal plane shifts to the left and, at 3 months of age, is ~ +65° (range: 0° to 125°). By older childhood, the normal mean QRS axis is –30° to +100°. In an older child, > +100° is right axis deviation (RAD), whereas < –30° is left axis deviation (LAD).

For older children, a quick and fairly accurate method to determine this is to just look at I and aVF. If both are prominent, you can quickly tell in which quadrant the mean vector lies. Visualize the following:

- Both (+) = Normal
- I (+) and aVF (–) = check for LAD
- Both (–) = Extreme axis deviation ("Northwest quadrant")
- I (–) and aVF (+) = check for RAD

LAD in children is most often associated with tricuspid atresia, atrioventricular septal defects (AV canal), and LVH. (Board question: In a newborn with Down syndrome having an ECG with lead I (+) and lead aVF (–), think atrioventricular septal defect; this newborn needs an echo!)

RAD causes include right ventricular hypertrophy (RVH) associated with congenital lesions (e.g., pulmonary stenosis [PS], atrial septal defect [ASD], tetralogy of Fallot [TOF], pulmonary hypertension, RBBB, or dextrocardia.)

RATES AND INTERVALS

OVERVIEW

The ECG is recorded on paper with a 1-mm^2 graph, displaying a thicker line every 5 mm. Because the paper moves at 25 mm/s, each thicker line is 1/5 of a second (or 0.2 sec—200 ms), and each mm represents 0.04 sec (40 ms). The interval covering 5 thicker lines (or 1 "big square") is 1 second.

There are a couple of quick ways to determine the heart rate. We'll discuss the RR interval, but know that any prominent wave of the standard QRS may be used to determine the interval. A quick and accurate method for determining heart rate: Calculate it as 1,500/RR interval in mm. So if the beat interval is 28 mm, the rate is 1,500/28 = 54 bpm. A less accurate but easier method is to divide 300 by the number of "big squares" in the RR interval. If the beat interval is 28 mm, this is not quite 6 big squares (since 6 x 5 mm = 30 mm). You divide 300 by 6 and get 50, but you know the heart rate is actually a little faster, because the interval is not quite 6 big squares. A derivative of this is the method in Dubin's book, *Rapid Interpretation of EKGs*, in which you memorize 2 sets of triplicates: 300–150–100 and 75–60–50. These are the corresponding heart rates for RR intervals of 1, 2, 3, 4, 5, and 6 big squares. (Remember: To do the math, divide 300 by the number of big squares; so 1 corresponds to 300, 2 corresponds to 150, etc.)

Normal heart rate for newborns is 100–160 bpm. Heart rate gradually decreases with age. Mean heart rate is > 120 during the first year of life. By age 3, it falls to ~ 110, and by age 5 it is ~ 100. By age 12, it is, on average, 85.

Sinus tachycardia in newborns is > 160 bpm and in children > 120 bpm. Sinus bradycardia again depends on the age: < 3 years, it is < 80; > 3 years, it is generally < 60. However, it is not uncommon to see heart rates of 50–60 bpm in normal teens and preteens, especially in athletic kids.

IMPORTANT INTERVALS

The PR interval indicates the time between atrial and ventricular depolarization; it is a reflection of mostly AV node conduction. Normal duration is 3–5 small squares (120–200 ms, because a "small square" is defined as 40 ms). In newborns, the PR interval is, on average, shorter than in older children, i.e., 130 ms or less, and increases gradually with age. A PR interval longer than 200 ms (1 big square) in teens and adults is the definition of 1° AV block. Intervals shorter than 120 ms (3 small squares) at these ages may indicate Wolff-Parkinson-White (short PR interval with delta wave), junctional rhythm (with retrograde P wave—see next), or left atrial overload (widened P wave—see next).

QRS duration is usually < 120 ms (i.e., 1/2 a big square).

QRS > 120 ms may be caused by:

- Bundle-branch block (right or left)
- Ectopic ventricular beat (PVC)
- Ventricular rhythm
- Ventricular pacemaker
- Drugs that prolong conduction (such as tricyclics)
- WPW
- Electrolyte problems (hyperkalemia)

The QT interval varies with heart rate. The QT interval corrected for heart rate is normally 340–440 ms (450 in girls). The formula used to calculate the corrected QT interval is: $QT_c = QT/ (RR)^{1/2}$. That is, the QT interval (in ms or sec) divided by the square root of the beat interval in seconds. Again: The R–R interval in this calculation must be in seconds. When scanning ECGs, a rule of thumb is: The QT interval normally is ~ 40% of the R–R interval; do the calculation for QT_c if it appears much shorter or longer. (For the Board exam, they will make it pretty obvious or will just tell you the patient has prolonged QT interval—you don't need to learn how to do square roots again by hand. ☺)

With prolonged QT_c, there is a tendency to develop recurrent syncope and/or sudden death, due to *torsades de pointes*. Prolonged QT_c has many causes. In a child without medications, it is most likely genetic or congenital prolonged QT syndrome. (Did the infant fail the newborn hearing screen? Long QT + sensorineural deafness = Jervell and Lange-Nielsen syndrome.)

The other etiologies for prolonged QT include:

- Tricyclic overdose (especially think about in the adolescent)
- Hypocalcemia

QuickQuiz

- In a 10-year-old, if the QRS is upright in I and down in aVF, what does this indicate about the axis?
- Know how to determine heart rates on an ECG tracing.
- What is the most common cause of prolonged QT interval in pediatrics?
- What prescribed drug may cause prolonged QT interval in a depressed adolescent?
- What P wave changes indicate left atrial hypertrophy? Right atrial hypertrophy?

- Hypomagnesemia
- Hypokalemia
- Type Ia and III antiarrhythmics (Ia = quinidine, procainamide; III = amiodarone, sotalol)
- Starvation with electrolyte abnormalities
- CNS insult

More recently discovered causes are:

1) Non-sedating antihistamines (these have been pulled from the market but may not be pulled from the Peds Boards), such as astemizole and terfenadine—their QT prolongation tendency can be increased by erythromycins, some azoles, such as ketoconazole, and hepatic dysfunction.
2) Liquid protein diet.

Treatment of long QT syndrome (LQTS) may include beta blockade, pacing, an implantable defibrillator, or rarely surgical sympathectomy.

The Brugada syndrome is a sodium channelopathy resulting in an RV conduction delay and ST elevation in V1–V3. Like LQTS Type 3, these patients have a sodium channel abnormality and are at risk for ventricular arrhythmia and sudden death. The only treatment is an implantable defibrillator.

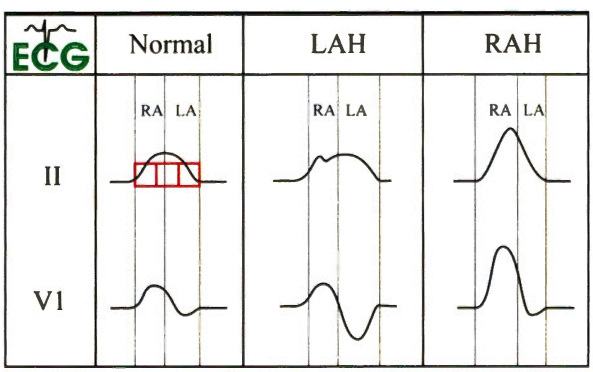

Figure 12-2: P Wave in Atrial Enlargement

Short QT_c may be caused by hypercalcemia and digitalis; it also just may be congenitally short (but can also cause ventricular arrhythmias)!

WAVEFORMS AND SEGMENTS

P WAVE

The P wave results from the depolarization of the atrium. The normal P wave is < 2 mm in height and < 120 ms (3 small squares) in duration, and the normal P wave axis is 0° to +90°. (Where else have you seen 120 ms? The normal PR interval is 120–200 ms, Figure 12-2.)

[If you don't have time, skip through these explanations, and just look for the "yellow highlighted" areas. This is mainly for those who want to understand "the way ECGs work."]

Most information from the P wave can be derived from II, aVR, and V1. As the wave of depolarization spreads from the SA node high in the right atrium, through the right, and then left atrial myocardium, the mean vector is downward and to the patient's left—so the normal P wave is positive in II and negative in aVR.

A retrograde P wave (i.e., a P wave not originating in the sinus node) is negative in II (and III and aVF) and positive in aVR—indicating an ectopic focus, originating in the inferior part of the atrium or at the AV junction, resulting in a wave of depolarization traveling toward aVR (picture this!). A retrograde P wave from the AV junction often results in a short PR interval.

Because atrial depolarization traverses from the patient's right to left, the normal P wave is positive in lead I, II, and aVF and is positive or biphasic in V1.

With right atrial preponderance (enlargement, hypertrophy, overload), the right atrial (initial) portion of the P wave is delayed and overlaps onto the left atrial portion of the P wave. The P wave width stays normal (< 120 ms), but look for an increased P wave amplitude in II (also true with III and aVF, but look only at II) and in V1 (the positive portion). Actually, the P wave "peaking" in II is more important than its height. So again, RA enlargement causes peaked P waves in II and V1 (Image 12-1)!

With left atrial overload, the left atrial component of the P wave is delayed, resulting in a wide P wave taking up most of the PR interval (i.e., < 120 ms). Other typical findings are a widened, notched P wave in II and an enlargement of the negative portion of the P wave in V1. The most

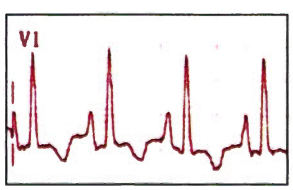

Image 12-1: RAE

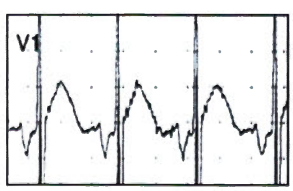

Image 12-2: LAE

sensitive ECG finding for left atrial enlargement is a broad negative P wave in V1, with duration of more than 40 ms (> 1 small square wide and 1 small square deep) (Image 12-2). On the other hand, the most specific ECG finding is a notched, "M" shaped P wave (usually in II) with an interpeak distance of > 40 ms.

Decreased P wave amplitude is seen in severe hyperkalemia.

T WAVE

The mean T wave vector changes rapidly and markedly after birth. The T waves are typically positive in V1 at birth. They remain positive for up to age 7 days, then invert in V1. The T wave should remain inverted in V1 until ages 9–10 years, and then they may be either inverted or upright in V1 during the teen years. If they remain positive after 7 days and up to 10 years of age, this may indicate right ventricular hypertrophy.

Peaked T waves can occur with:

- Hyperkalemia
- Intracerebral hemorrhage

U WAVE

U wave occurs just after the T wave and is mainly something to look at in adults or older adolescents. It is usually small and best seen in V2–V3. If seen, it is usually a < 1 mm, rounded deflection in the same direction as the T wave. If the U wave is prominent, there is an increased tendency for *torsades de pointes* (if the U wave is > 50% of the height of the T wave, you should include it in your QT interval measurement). You see prominent U waves with hypokalemia, bradycardia, digitalis, and amiodarone.

ST SEGMENT

There are 3 main causes of ST segment elevation: acute MI, Prinzmetal angina, and pericarditis—obviously, the first 2 are almost never seen in children. Therefore, pericarditis is the most common cause of cardiac chest pain in pediatrics, and it affects the whole heart; so you should see ST changes in most leads. You may also see it in something called normal, "early repolarization variant," intracerebral hemorrhage, hypertrophic cardiomyopathy, LVH, LBBB, cocaine abuse, myocarditis, and hypothermia.

ST segment depression occurs in pediatrics with:

- Subendocardial ischemia (especially if down-sloping or flat), such as with classic angina in adults
- LVH with strain (ST depression with flipped T waves in left precordial leads)
- RVH, which may cause RAD and ST segment depression preceding a flipped T wave in V1
- Digitalis effect
- Hypokalemia

QRS COMPLEX

QRS complex. Depolarization of the ventricles occurs simultaneously after the depolarization of the interventricular septum. The normal mean vector of depolarization of the interventricular septum points from the patient's left to the right, across the septum. This is seen as a small, initial deflection, which is positive in V1 (R wave) and negative in V6 (Q wave). A septal Q wave in V6 generally means normal initial depolarization.

The left ventricle is normally much more massive than the right ventricle, and, therefore, the mean QRS vector (reflecting depolarization of the ventricles) is strongly to the patient's left. You see a large negative deflection in V1 and positive deflection in V6. On the frontal plane, as mentioned above, the mean vector is –30° to +100°.

The normal duration of the QRS is < 120 ms.

We discuss QRS changes with ventricular hypertrophy and conduction disturbances in the next 2 topic areas.

VENTRICULAR HYPERTROPHY

LVH

Left ventricular hypertrophy is age-dependent. In infancy, LVH will result in the mean QRS being moved to the left and posteriorly. In the frontal plane, the QRS axis may move to 0° to 60°; < 30° in an infant is very uncommon and suggests LVH. The leftward shift of the QRS axis increases the R wave and decreases the S wave in V5 and V6—and the posterior shift of the QRS axis results in a decrease in the R wave and an increase in the S wave in V1.

Without an axis shift to help you, base the diagnosis of LVH mainly on voltage changes. R waves less than the 5th percentile or S waves more than the 95th percentile in V3R and V1 suggest increased posterior forces. Also look for R waves more than the 95th percentile in V5 and V6. On a Board question, they'll have to give you a graph or the values. You won't need to memorize these for individual ages.

In older adolescents and adults, LVH causes a prolonged activation of the myocardium. LVH causes an exaggerated negative deflection in V1 and a positive deflection in V6. (See Image 12-3, LVH.)

Although the specificity of the various ECG criteria for LVH is pretty good (~ 95%), the sensitivity is low and varies from 25% for simple addition criteria, to 50% for a complicated point system. Note: If the prevalence of LVH in a population is 5%, there will be many more false negatives and many more false positives than true positives.

You may see a left ventricular "strain" pattern with LVH. LV strain presents with ECG changes that are

QuickQuiz

- When do you find peaked T waves?
- What effect may hypokalemia have on the ST segment?
- True or false? In a term infant, RVH is a common finding and considered "normal" on a standard ECG.
- How does LVH present on the ECG? RVH?

precordial, ST segment depression, and flipped T waves (particularly in inferior and lateral leads) in a patient with ECG criteria for LVH. (Is there a negative T wave in lead V6 after 7 days of life? If so, think LVH!)

RVH

The term infant has a right ventricular wall that is as thick as or thicker than the left ventricle and has physiologic "normal" right ventricular hypertrophy. For pathologic excessive RVH, the mean QRS will move farther right and anteriorly. This results in frontal plane QRS axes > 190° for infants < 1 week of age or 135° for infants > 1 month of age. RVH will produce taller R waves, with smaller S waves in right chest leads, and smaller R waves and larger S waves in left chest leads (Image 12-4).

Also look for a "pure" R wave, R > 25 mm voltage, or a qR pattern in the right chest leads—this suggests pathologic RVH in the newborn. It is also highly suggestive of RVH if you see an upright or even a "flat" T wave in V4R and V1 in a child between 1 week and 8 years of age.

In older adolescents and adults, ECG criteria for RVH are right axis deviation, increased R voltage in V1 or S in V6, and rsR' in V1, and again, because of repolarization changes, ST segment depression and a flipped T wave in V1, sometimes in V2. The ST segment depression and flipped T wave generally indicate RV stress/hypertension.

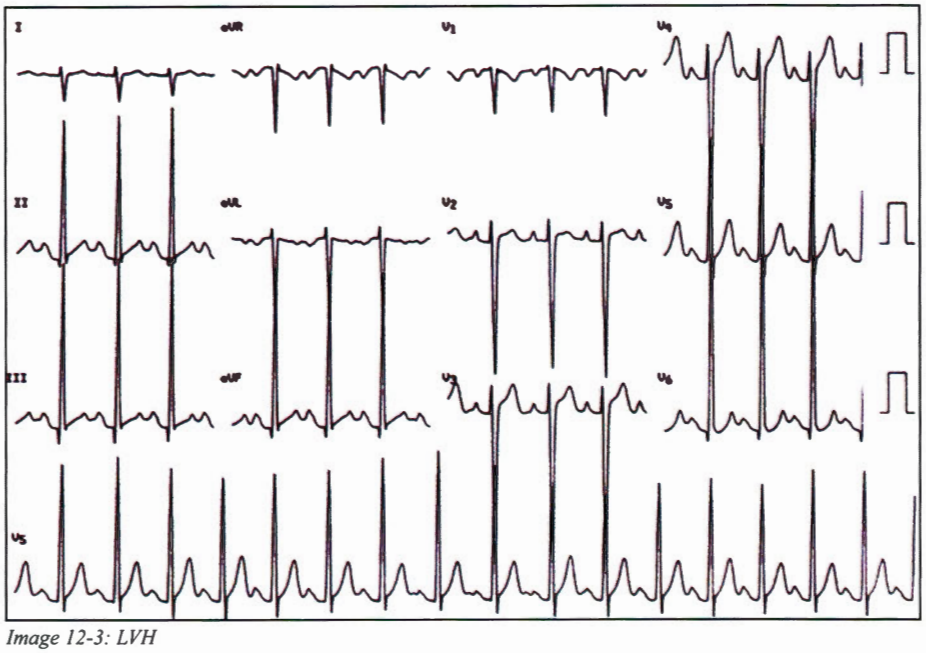

Image 12-3: LVH

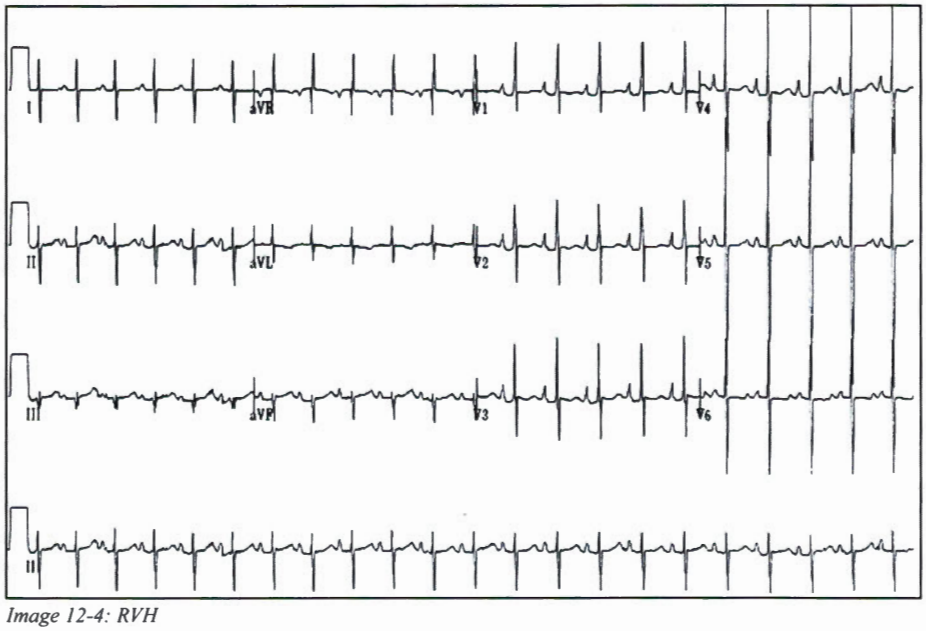

Image 12-4: RVH

CONDUCTION DISTURBANCES

ATRIOVENTRICULAR (AV) BLOCKS

Atrioventricular blocks:

- 1° AV block prolongs the PR interval more than normal for age and by > 200 ms (1 big square) beyond 16 years (Image 12-5).
- 2° AV block results in 2 main patterns:
  - Mobitz I: Wenckebach phenomenon involves progressive prolongation of the PR interval until there is a drop in QRS (ventricular beat) (Image 12-6). This effect is primarily from vagal tone on the AV node and is generally not considered malignant. Occasional follow-up is recommended. This rarely requires treatment.
  - Mobitz II: Normal PR intervals, but, periodically, there is a drop in QRS. 2:1 AV block is 2 P waves for each QRS; 3:1 is 3 P waves for each QRS, etc. (Image 12-7). Mobitz II and higher-grade heart block implies disease of the His-Purkinje conduction system and is an abnormal finding. This often requires a pacemaker.
- 3° AV block or complete heart block: No atrial depolarizations are conducted through the AV node. The P wave and QRS have independent regular rhythms at differing rates (AV dissociation). If the QRS complex has a normal width (< 100 ms), there is a junctional ectopic pacemaker. Junctional escape rate is 40–60 bpm, whereas ventricular escape rate (which also would be a wider QRS) is 20–40 bpm. Note: the AV node has no pacemaker activity. Junctional pacing originates from the myocardial tissue at the AV junction (Image 12-8).

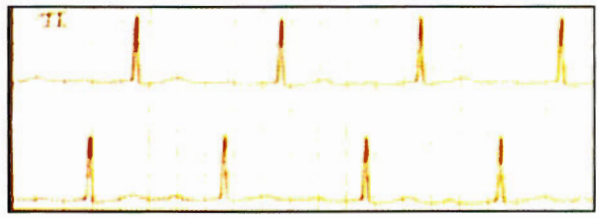

Image 12-5: 1° AV Block

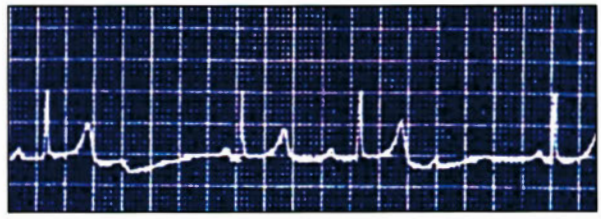

Image 12-6: 2° AV Block, Mobitz I

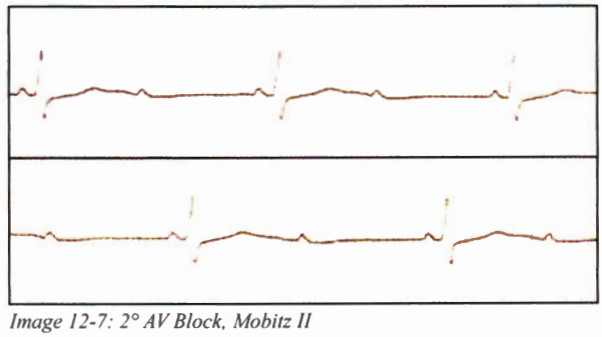

Image 12-7: 2° AV Block, Mobitz II

BUNDLE-BRANCH BLOCK

BBB Review

Just a little beyond the AV node, the bundle of HIS fast conduction pathways splits in two. These 2 fast conduction pathways travel down the interventricular septum, and one (the right bundle branch) then goes to the right ventricle, while the other one (the left bundle branch—functionally, if not anatomically) splits again and proceeds to the anterior and posterior sections of the left ventricle. If conduction in one of these pathways is blocked, the depolarization downstream to that pathway is delayed because the myocardial tissue in that area must wait for the depolarization wave from much more slowly conducting, adjacent, myocardial tissue.

LBBB

Left bundle-branch block (LBBB) is rare in children and is more common in adults. The QRS is prolonged, with a duration of 120–180 ms (3–4.5 small squares). Because

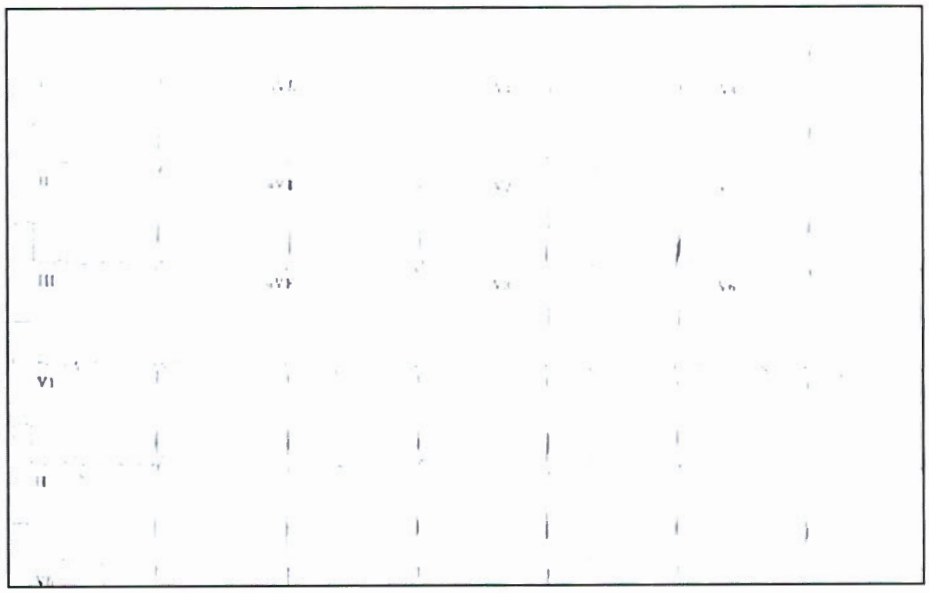

Image 12-8: 3° AV Block with Junctional Ectopic Pacemaker

QuickQuiz

- Differentiate Mobitz I from Mobitz II.
- With 3° AV block, what type of pacemaker is reflected in a narrow QRS complex? What does a wide QRS complex reflect?
- Under what conditions do you see "rabbit ears" on an ECG?
- Which children require a pacemaker for sick sinus syndrome? For heart block?

the left ventricle depolarization is now transmyocardial, it is depolarized over a longer period, resulting in an RR' (notched or slurred) in the lateral leads (I, aVL, and V6), and there is a corresponding SS' (also called QS) in V1. 50% of patients have a normal axis; 50% have LAD (–30° to –90°).

RBBB

Right bundle-branch block (RBBB) is more common in children, particularly after open heart surgery: The direction of septal depolarization is normal—left-to-right, but the right ventricle is depolarized over a longer period, resulting in an RR' or RSR' ("rabbit ears") in V1 and a wide S wave in V6. Visualize how the RSR' in V1 is formed: The initial R wave is due to normal, left-to-right septal depolarization, the S is depolarization of the left ventricle, and the final R' is due to the delayed depolarization of the right ventricle. In V6, the S wave is due to delayed depolarization of the right ventricle. This is often present after cardiac surgery (Image 12-9).

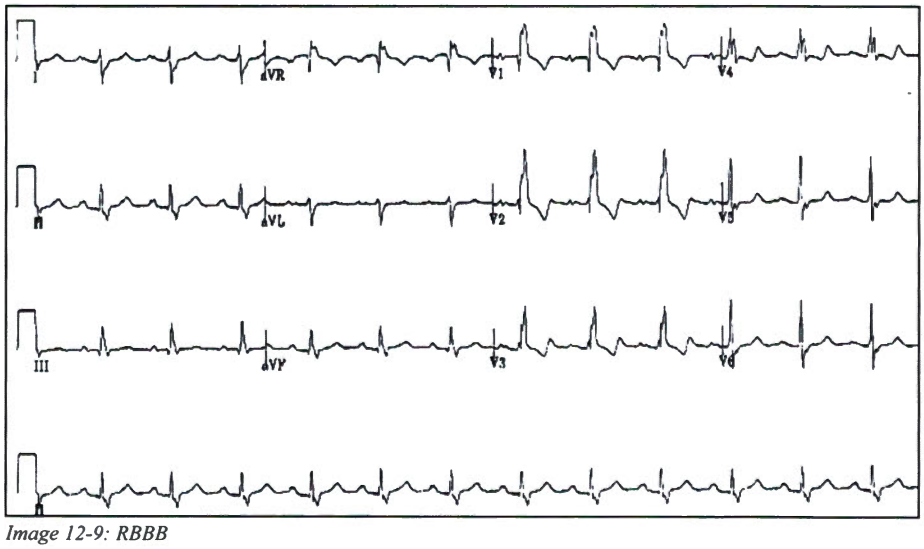

Image 12-9: RBBB

ARRHYTHMIAS

MECHANISMS OF ARRHYTHMIAS

The 2 usual mechanisms of abnormal rhythms are reentry and automaticity. The reentrant mechanism is the cause of most abnormal rhythms. Reentry refers to abnormal "loops" of electricity causing arrhythmias. Atrioventricular reentry (accessory bypass tract) is the leading cause of supraventricular tachycardia (SVT) in infants and young children; AV node reentry is the second leading cause in children (AV node reentry is the leading cause in adolescents and adults). Automatic rhythms are accelerated ectopic rhythms (i.e., a focus in the heart is causing the arrhythmia). Parasystole is a 3rd mechanism, which is a rare cause of PVCs. Be able to diagnose all rhythms at a glance.

SICK SINUS SYNDROME

Sick sinus syndrome (sinus node dysfunction) may manifest as one or more of the following: abnormal sinus bradycardia, sinus pauses, sinus blocks, sinus arrest, dominant escape rhythms, and tachy-brady syndrome. These patients usually do not need electrophysiologic testing.

Because prognosis is good, there are only 2 indications for treatment with a pacemaker in children with sick sinus syndrome:

1) The patient is symptomatic (e.g., syncope).
2) The patient has tachyarrhythmias requiring therapy, which might precipitate significant bradycardia.

Look for this in a child who has had atrial surgery—ASD repair (particularly the sinus venosus or "high" atrial septal defect), atrial baffles in transposition of the great vessels (e.g., Mustard operation), or the Fontan procedure.

Note: If an ECG presents with sinus bradycardia in an adolescent female, don't forget that patients with anorexia nervosa will have slow heart rates. This is not true sick sinus syndrome but may look similar to it. Treat the underlying condition and the bradycardia will improve.

HEART BLOCK

Heart block: Permanent pacing is indicated for symptomatic 2nd degree (Mobitz II) and most 3rd degree heart blocks. Patients with congenital complete heart block can

remain well and asymptomatic for years. Emergency treatment consists of transcutaneous or transvenous pacing, IV atropine, isoproterenol, or other medications.

SUPRAVENTRICULAR TACHYCARDIAS

Atrial Flutter

Atrial flutter has an atrial rate of 230–420 bpm (up to 500 bpm in newborns), usually with a 2:1 AV block. It is usually due to reentry within the right atrium and around the tricuspid annulus. Isolated presentation in a healthy newborn is occasionally seen. In older patients, it is almost always an indication of disease, most often either organic heart disease or pulmonary disease. Atrial flutter may spontaneously convert to either atrial fibrillation or a normal sinus rhythm. Vagal maneuvers slow the rate and allow better diagnosis. Rule out pulmonary emboli (often multiple) and thyroid disease, especially if there is no identifiable heart or lung history. The normal block is 2:1. If it is ≥ 3:1, the cause is either AV node disease or drugs. For acute atrial flutter in infants < 1 year of age, do not use verapamil, because it may cause heart failure or hypotension (Image 12-10).

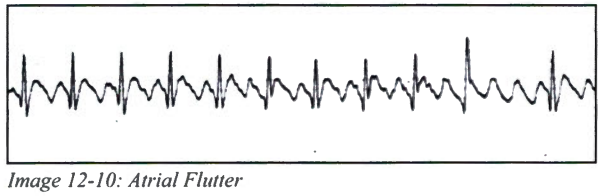

Image 12-10: Atrial Flutter

The most effective treatment for atrial flutter is synchronized electrical cardioversion. (Systemic embolization may occur but is less common in atrial flutter than in atrial fibrillation.) Low energy can be used (0.5 J/kg or 10–50 Ws in older adolescents/adults). Higher energy (1–2 J/kg or 100–200 Ws in adults) is often used because it has less of a tendency than low energy to convert the rhythm to atrial fibrillation. Always shock if the patient is hemodynamically compromised. Overdrive pacing is also effective in more stable patients.

Use antiarrhythmic drugs for nonemergent cardioversion. Typically, you can control the rate by slowing AV node conduction with IV diltiazem, digoxin, or a beta-blocker; you can attempt conversion of the atrial rhythm with other agents, such as procainamide, flecainide, ibutilide, sotalol, or amiodarone—depending on the clinical situation. Ibutilide (Corvert®) is a new class III antiarrhythmic (IV only), which is particularly effective in adults for rapid cardioversion with minimal hemodynamic effects. Quinidine is a viable option but is not used much anymore. Use quinidine, flecainide, sotalol, amiodarone, and dofetilide to prevent recurrence. Dofetilide is also a newer class III oral agent. These drugs can prolong the QT interval.

Radiofrequency catheter ablation or cryoablation is a treatment modality that can cure the most common types of atrial flutter; these treatments are used for persistent or recurrent atrial flutter.

Atrial Fibrillation

Atrial fibrillation (AF) usually has an irregular ventricular rate of 130–200 (about the same as the ventricular rate of atrial flutter with a 2:1 AV block) and is rare in children (Image 12-11). With new-onset AF, or in AF unresponsive to the usual treatment, consider hyperthyroidism, hypomagnesemia, alcoholism/cocaine abuse, and excessive caffeine and nicotine as possible causes.

Anticoagulate for 3 weeks before cardioversion if the patient is stable, and continue to anticoagulate for at least 6 months after successful cardioversion.

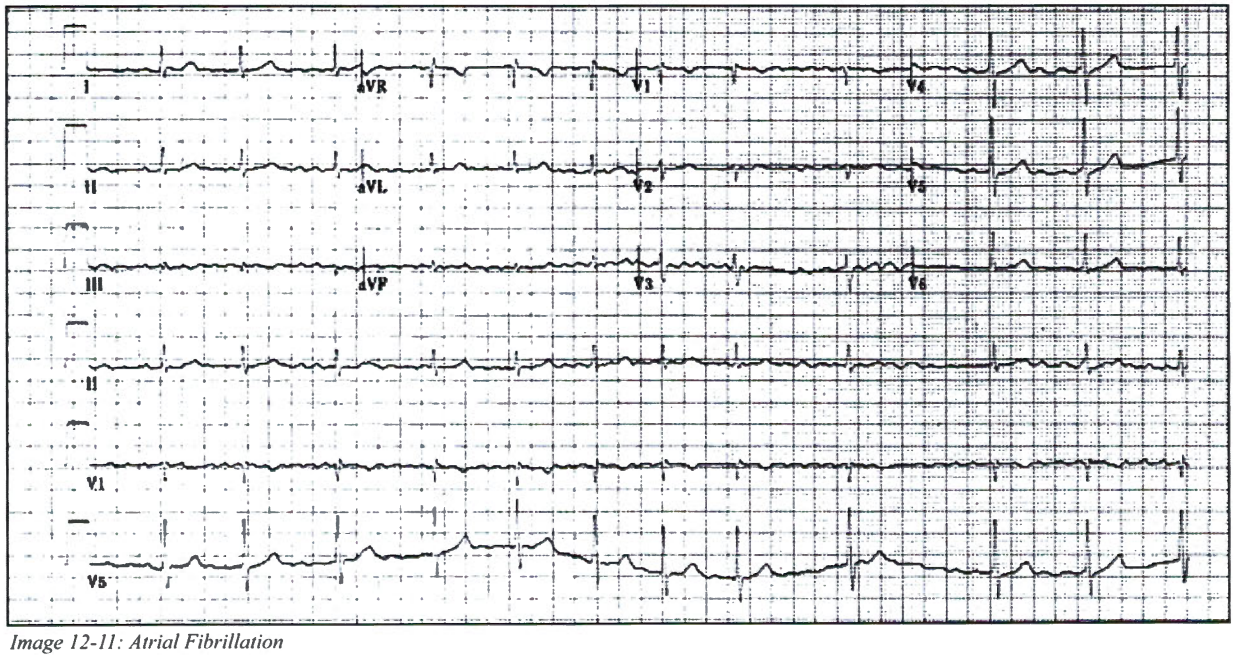

Image 12-11: Atrial Fibrillation

Quick Quiz

- What is the treatment for atrial flutter?
- What antiarrhythmic drugs can you use for nonemergent conversion of atrial flutter?
- What is the leading cause of PSVT in children?
- A stable infant presents with PSVT. What are the possible treatments? What if the infant is unstable?

You can usually treat the rapid ventricular response of chronic AF with digoxin, but also consider diltiazem, verapamil, or beta-blockers if the heart is healthy (i.e., can tolerate the negative ino-/chronotropic effects). Patients have better exercise tolerance on verapamil. These agents do not convert the abnormal rhythm; they just slow the ventricular rate!

To medically convert, after the rapid ventricular response is controlled, give dofetilide, quinidine, procainamide, flecainide, disopyramide, propafenone, sotalol, or low-dose amiodarone. IV ibutilide or amiodarone is effective in terminating acute AF.

Paroxysmal Supraventricular Tachycardia (PSVT)

Most paroxysmal SVT (PSVT = PAT) episodes are due to a reentrant rhythm. This is the most common supraventricular tachycardia in children. Rate is 150–280 bpm (same as or slightly faster than AF or A-flutter). Usually the P wave is not visible (buried in the QRS); but if seen, it usually is retrograde. If the monitor shows narrow complexes, treat with vagal maneuvers (diving reflex in infants—place ice bag to face for 10–20 seconds), adenosine, or verapamil (avoid verapamil in infants < 1 year of age!). Adenosine (Adenocard®) is the drug of choice because of its effectiveness and very short half-life (~ 10 seconds). It works on the AV node, with transient AV block, which is involved in most of the SVTs (Image 12-12).

Note: In an emergency situation with an unstable infant, treat with D/C cardioversion.

Many antiarrhythmic drugs also are effective for chronic treatment, including digoxin, beta-blockers, calcium channel blockers, class III agents, and class Ia agents. Flecainide (Ic) is approved for SVT, but most try something else first. Radiofrequency catheter ablation or cryoablation can cure PSVT. Differential diagnosis of wide complex tachycardia includes PSVT with aberrant conduction, PSVT with resting BBB, and V-tach (see below).

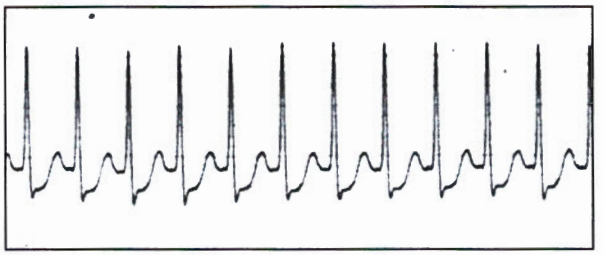

Image 12-12: PSVT

WPW

Wolff-Parkinson-White (WPW; pre-excitation syndrome): PR interval is < 0.12 seconds due to a delta wave (Image 12-13). Total QRS is > 0.12 seconds because of the fusion between the normal QRS and pre-excited depolarization, which bypasses the AV node. This bypass tract (Kent bundle) is faster than the AV node, and therefore, a portion of the electrical current reaches the ventricle sooner (the delta wave on the ECG) and pre-excites the ventricle. Another name for WPW is "pre-excitation syndrome." Often, the accessory pathway is concealed, and the delta wave will not be visible when the patient is in normal sinus rhythm. An uncommon association of WPW is Ebstein anomaly of the tricuspid valve.

Treatment of WPW: Many patients have completely asymptomatic WPW and no dysrhythmias. Treat patients with WPW and a narrow complex tachycardia (rate is usually ~ 180–240) with vagal maneuvers, cardioversion, procainamide, verapamil, or adenosine—same as any SVT! But … never treat acute AF or A-flutter

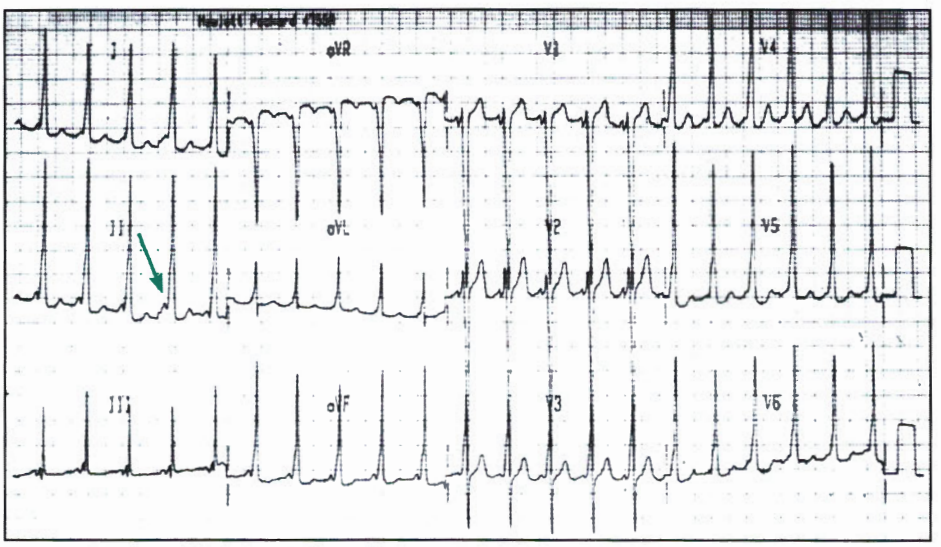

Image 12-13: WPW with Delta Waves (arrow)

(which usually has a wide QRS) in the setting of WPW with digoxin, verapamil, or beta-blockers. Although verapamil and digoxin increase the refractory period in the AV node, they can decrease the refractory period in the bypass bundle! This can result in rapid-rate transmission to the ventricle, fibrillation, and/or sudden death.

Instead, treat acute AF or A-flutter in WPW with IV procainamide. [Know!] Shock if there are any signs of hemodynamic deterioration in any WPW tachyarrhythmia; especially watch those with pulse rate > 285, because they are at greatest risk of V-fib.

Radiofrequency ablation is now considered by many to be the treatment of choice for older children and adults with SVT and WPW and occasionally for AF!

Note: Most electrical cardioversion of SVTs can be terminated with low energy: 25–50 Ws. The exception is AF, which usually requires > 100 Ws.

VENTRICULAR ARRHYTHMIAS

PVCs

PVCs often have a compensatory pause; that is, they do not reset the sinoatrial node (i.e., the time between the sinus beats that are on either side of the PVC = 2 basic RR intervals). You do not need to treat asymptomatic, simple PVCs (even if the patient has thousands each day). Simple PVCs occur beyond the T wave, are uniform, and have constant coupling (reentrant) (Image 12-14). Also, do not treat complex PVCs (pairs, triplets) if the patient is asymptomatic and has no underlying heart disease!

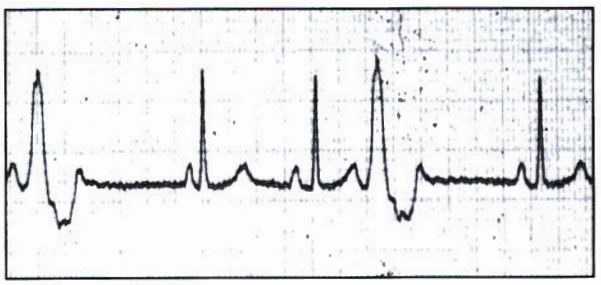

Image 12-14: PVCs

(Did they give you a clue that the patient may have tuberous sclerosis? Cardiac tumors can cause multiple types of PVCs, and cardiac rhabdomyomas are associated with tuberous sclerosis.)

Ventricular Tachycardia

Ventricular tachycardia is defined as 3 or more sequential PVCs occurring at a regular rate of ≥ 120 bpm. Most occur at a rate of 150–200. Differential diagnosis includes SVT with aberrant conduction, WPW, SVT with RBBB or LBBB, and severe hyperkalemia causing very large, peaked T waves (Image 12-15).

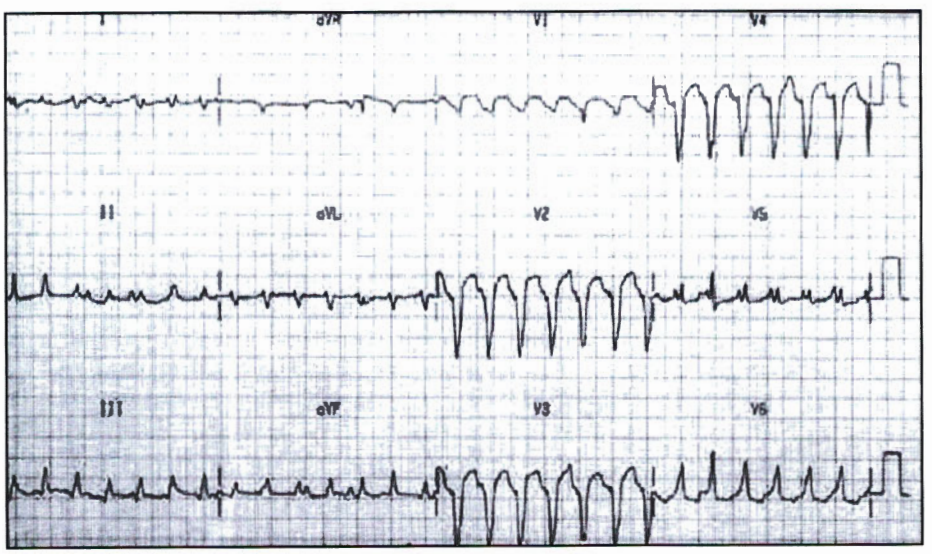

Image 12-15: Ventricular Tachycardia

A benign form of ventricular tachycardia is accelerated ventricular rhythm. This may present in infants or older children as a slow V-tach at the same or slightly faster rate as the underlying sinus rhythm. The patients are asymptomatic, and this tachycardia usually does not respond to drugs and needs no treatment. It may resolve over time.

In pediatrics, V-tach is most commonly due to:

- Electrolyte disturbances
- Myocardial disease, particularly myocarditis or hypertrophic cardiomyopathy
- Ion channel disorders (long QT syndrome)
- Postoperative states
- Ingestions
- Hypoxia or ischemia
- Idiopathic

If the V-tach lasts longer than 30 seconds or is unstable, it is usually due to organic heart disease. These patients have a high risk of sudden death; therefore, because of this danger, immediately use electrocardioversion in any patient with a wide QRS tachycardia and hemodynamic deterioration (treat like V-fib). If the patient is stable, you can use lidocaine, procainamide, or amiodarone (amiodarone is now preferred in ACLS and PALS protocols). Do not ever use verapamil with any wide complex tachycardias in the emergency setting (30% of those with ventricular tachycardia rapidly deteriorate!!). V-tach, which is consistently induced by exercise, is often well controlled by beta-blockers. Other V-tachs may require

Quick Quiz

- What is the drug of choice for an infant with WPW who develops atrial flutter?
- What is the treatment (if any) for simple PVCs?
- What treatments can you use and what can you not use for ventricular tachycardia?
- For which patients should you not use verapamil to slow the heart rate?
- When is it OK to use verapamil to slow the AV nodal conduction?

electrophysiologic testing. V-flutter appears as a sine wave at 150–300 bpm.

Torsades de pointes (Image 12-16) is often associated with a prolonged QT interval and a prominent U wave. Don't forget about the prolonged QT syndrome as an etiology. Also, quinidine, procainamide, other Class Ia antiarrhythmics, and tricyclics are common causes. You may also see it in association with very low K^+ or Mg. Treat associated bradycardia acutely by increasing the atrial rate with isoproterenol or overdrive pacing. Mg sulfate is another treatment option. Shock for sustained *torsades de pointes* because the patient will be unstable. Do not give quinidine or procainamide—any Class Ia antiarrhythmic worsens *torsades de pointes*. [Know!]

[Also know] Avoid verapamil with:

- Young infants
- Atrial fib occurring in WPW
- Atrial flutter
- Wide complex tachycardias
- Beta-blockers—relative contraindication because they are both negative chronotropes and negative inotropes

Okay to use verapamil (but never in infants!):

- To control the ventricular response to AF in an otherwise healthy heart
- For PSVT (2nd choice after adenosine)

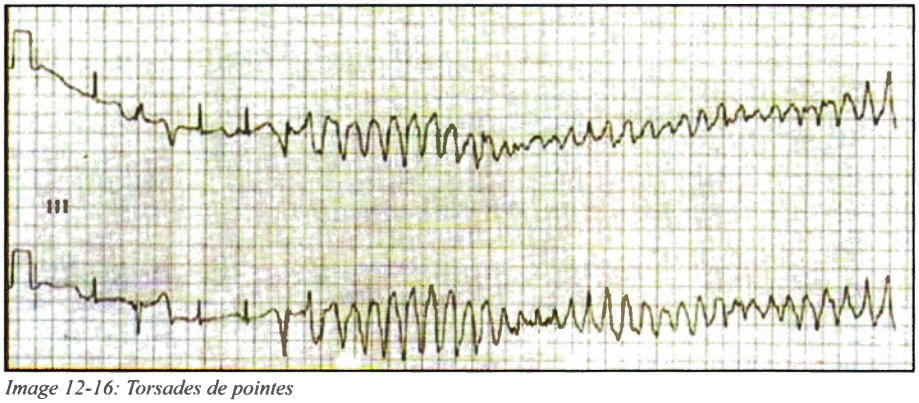

Image 12-16: Torsades de pointes

Cardiac Pacing

Temporary pacing: Single- or dual-chamber temporary pacing leads can be placed transvenously. Dual-chamber pacing is usually better but is not essential in emergency, temporary settings.

Permanent pacing is used for chronic, symptomatic sinus bradycardia and for complete heart block.

The most common dual-chamber pacemaker is called a DDD. Most clinicians use this one unless the patient is in chronic, slow atrial fibrillation. The DDD is the most physiologic and provides better exercise tolerance.

ANTIARRHYTHMIC DRUGS

With antiarrhythmic drugs (A-ADs), always wait 4–5 half-lives before determining whether a drug is effective. All A-ADs have a proarrhythmic potential.

Class I: Decreases upslope of the action potential (i.e., slows conduction primarily by blocking sodium channels).

Ia: Quinidine, procainamide, disopyramide

Ib: Lidocaine, tocainide, mexiletine, phenytoin

Ic: Flecainide and propafenone

Class II: Decreases sympathetic activity—beta-blockers.

Class III: Prolongs the action-potential duration—amiodarone, sotalol, bretylium, and the newer agents, dofetilide (Tikosyn® orally), and ibutilide (Corvert® IV).

Class IV: Blocks slow inward Ca^{+2} current: calcium channel blockers, especially verapamil and diltiazem.

Note: Adenosine is not in the previous grouping. It slows conduction in the SA node and AV node; it is used for conversion of SVT (AV node reentry and WPW) to normal sinus rhythm. It also induces coronary artery vasodilation and is used in cardiac perfusion imaging and stress echocardiography. Adenosine depresses LV function but has such a short half-life, you can use it in patients with decreased LV function. Acute shortness of breath following adenosine can be related to bronchoconstriction; if the Boards ask you what to do next, look for a bronchodilator in the choices (e.g., terbutaline).

Major side effects of the A-ADs [Know]:

- Ia:
  - Quinidine prolongs the QRS complex and the QT interval—occasionally leading to *torsades de pointes*, diarrhea, and (rarely) autoimmune thrombocytopenic purpura. Also "cinchonism": hearing loss, tinnitus, and psychosis.
  - Procainamide prolongs QT and QRS, but also causes blood dyscrasias, such as agranulocytosis, neutro-penia, and thrombocytopenia, in ~ 0.5%. It also causes drug-induced lupus and must be used with caution in heart failure patients because it has a mild, myocardial depressive effect.
- Ib: Lidocaine: Seizures.
- II: Beta-blockers are commonly associated with bradycardia and can potentially aggravate asthma.
- III:
  - Bretylium: transient hypertension, then postural hypotension.
  - Amiodarone is the most effective drug, but also, due to the extremely high iodine content (the most toxic anti-arrhythmic drug in adults), do not use it chronically in children without supervision by a specialist. It has an extremely long half-life (40–55 days). Amiodarone is associated with:
    - Corneal deposits
    - Hyper/hypothyroidism
    - Pulmonary fibrosis
    - Hepatic toxicity
    - Gray skin
    - Sun sensitivity

    It does not cause hematologic changes. Pulmonary fibrosis can be severe and is fatal 10% of the time, but it is very rare in children.
- Other: Digoxin: arrhythmias. Digitalis toxicity is more likely in those with low K^+ or high Ca^{+2}.

Determine the toxic levels of both digoxin and quinidine by changes in the ECG, not by serum levels.

CONGENITAL HEART DISEASE

OCCURRENCE / CAUSES

Congenital heart disease occurs in ~ 7–8/1,000 live-born infants and has a much higher incidence in those who die *in utero*. VSD is the most common congenital heart lesion; pulmonic stenosis, ASD, and PDA are the next most common.

Genetic conditions are associated with specific cardiac defects. They are listed in Table 12-1.

[Know these associations!] Environmental factors can be important, too. Lithium use by the pregnant woman is associated with Ebstein anomaly of the tricuspid valve. Other drugs to be wary of during pregnancy are progesterone, alcohol (use has been associated with fetal alcohol syndrome and left-to-right shunts), and retinoic acid. Women with diabetes are at increased risk for having infants with congenital heart disease and a temporary form of hypertrophic cardiomyopathy.

Table 12-1: Genetic Diseases and Their Associated Cardiac Abnormalities

I. Single Mutant Gene Syndromes (Autosomal Dominant, Recessive, or X-linked)	
Noonan syndrome	Pulmonic stenosis Hypertrophic cardiomyopathy
Apert syndrome	VSD Coarctation of the aorta
Holt-Oram syndrome	ASD VSD
Alagille syndrome	Pulmonic stenosis
Ellis-van Creveld syndrome	Single atrium
II. Chromosomal Abnormalities	
Cri-du-chat syndrome	VSD
Turner syndrome (XO)	Bicuspid aortic valves Coarctation of the aorta
Trisomy 21 (Down syndrome)	Endocardial cushion defect
Trisomy 13 syndrome	VSD
Trisomy 18 syndrome	VSD

LEFT-TO-RIGHT SHUNTS

Overview

Left-to-right shunts are defined as defects where systemic circulation is shunted to the pulmonary circulation by an abnormal conduit (Table 12-2).

What determines the impact of a left-to-right shunt? Generally, 3 factors are important:

1) Size of the communication
2) Pressure differences between the 2 vessels/areas shunted
3) Total outflow (or vascular bed) resistances

If the communication is restrictive (i.e., small in size), flow will be very much reduced, and it really doesn't matter what the pressure or outflow resistances are. For atrial shunts, the pressures are low and almost equal, so outflow resistance and ventricular diastolic pressures (left ventricular end-diastolic pressure is usually greater than right ventricular end-diastolic pressure, so normally there is a left-to-right flow across the ASD) will be the determining factors.

QuickQuiz

- True or false? Serum digoxin concentration is usually helpful in determining toxicity.
- Know Table 12-1.
- Lithium use during pregnancy is associated with what cardiac abnormality?
- Describe the murmur of PDA.
- What is the therapy for PDA?
- What is the most common congenital heart defect in term newborns?

At birth, systemic and pulmonary resistance and pressures are high and equal, and there will be little shunting from left to right; however, as systemic vascular resistances increase, pulmonary vascular resistance decreases over 4–8 weeks; and thus, a large left-to-right shunt can develop once pulmonary vascular resistance has fallen below systemic resistance/pressure—after a few days or weeks.

For VSD or PDA, where the communication is large, systolic pressures will be equal on both sides of the conduit; thus, the relative vascular bed ("outflow") resistance of each side of the shunt will determine the direction of shunting. If left-sided vasculature resistance is higher than the right side, there will be a left-to-right shunt.

The persistence of high flow and pressures in the pulmonary arteries may lead to progressive and permanent, or fixed, elevation of pulmonary resistance and subsequent right-to-left shunting and cyanosis (Eisenmenger syndrome). This can be lethal.

Table 12-2: Left-to-Right Shunts Occurring in "Post-Tricuspid" Valve

Aorta to pulmonary artery shunts:
PDA
Hemitruncus arteriosus
Coronary-pulmonary fistula
Left coronary artery anomalously originating from pulmonary artery
Aorta to right ventricle:
Sinus of Valsalva fistula
Coronary arteriovenous fistula
Aorta to right atrium or vena cava:
Systemic arteriovenous fistula
Sinus of Valsalva fistula
Left ventricle to right ventricle:
VSD
Endocardial cushion defect
Left ventricle to right atrium:
Left ventricle to right atrium connection
Endocardial cushion defect

Patent Ductus Arteriosus (PDA)

The ductus arteriosus normally closes "functionally" within 10–15 hours after birth, but complete anatomic closure may not occur for 3 weeks. Closure occurs by constriction of smooth muscle in the ductus arteriosus. Premature infants (weighing < 1,750 g) have clinically apparent PDA ~ 40–70% of the time. Most feel that 2 of the mechanisms responsible are the inability of the ductus arteriosus in premature infants to respond normally to increased oxygen tensions and to the changes in prostaglandin levels that occur at birth.

Clinically, the child presents with a continuous murmur (think about it—the aortic pressures will never be below pulmonary artery pressure, so blood will continuously flow from aorta to pulmonary artery through the ductus). It is described as a "rumbling" or "machinery-like" murmur and will usually increase in intensity in late systole. You can hear it best below the left clavicle. If the PDA is small, the murmur is all that may occur. If it is large, the PDA increases LV output and will increase stroke volume, which causes a rise in aortic pulse pressure. Since flow continues during diastole, you get a low diastolic pressure and a "collapsing" or bounding pulse. The increased volume will result in increased left atrial and ventricular sizes, and the CXR and ECG may show evidence of hypertrophy. CXR will also show increased pulmonary markings because of the increased blood flow; eventually, irreversible pulmonary hypertension (Eisenmenger syndrome) can develop.

Echocardiogram is the best diagnostic test.

In an asymptomatic child, close a PDA either by catheter techniques or surgically. In premature infants, indomethacin therapy is used with 80% success. Even if the child is older and has no symptoms, signs, or problems from the PDA (so called "silent PDA"), some would close the PDA to prevent endocarditis of the ductus—but with the new endocarditis guidelines this is controversial (since patients with ductus do not receive prophylaxis anymore for dental procedures, etc). Latest guidelines suggest discussion between physician and patient of the risks and benefits. Transcatheter closure with a coil can be successful if the diameter of the ductus is < 5 mm, with the larger ductus needing surgery or other device closure. For further newborn management issues, see The Fetus & Newborn section.

Ventricular Septal Defect

Ventricular septal defects (VSDs) are the most common congenital heart defects and make up 25–30% of cases of congenital heart lesions in term newborns.

VSDs usually occur as isolated abnormalities but can occur with other congenital cardiac abnormalities. At

birth, a majority of VSDs occur in the muscular septum, but these usually close spontaneously ≤ 1 year of age. After 1 year, the majority of VSDs detected occur in the membranous septum. (So, just to reiterate a favorite Board question topic: < age 1 year, most are in the muscular septum; > age 1 year, most are in membranous septum—below the tricuspid and the aortic valves).

Clinically, VSD is initially detected by finding a murmur, which is usually described as "harsh" or high-pitched. (On the Boards: An infant presents at 3–4 weeks with "breathing harder" and a new murmur. Think VSD. Remember: As the pulmonary resistance drops over the first month of life, more blood flows across the VSD leading to congestive heart failure [CHF].) If the shunt is small, you may hear it only in early systole, but, as it increases in size, it becomes holosystolic and ends with aortic valve closure of the second sound. Intensity is not related to size of the defect—loud murmurs can be heard with insignificant VSDs (known as *maladie de Roger*). Palpable thrills are common.

You can usually hear the murmur best at the lower left sternal border as it radiates through the precordium, with maximal intensity near the subxiphoid area. Variations can occur depending on where the VSD is. For example, a high subpulmonic VSD will result in a middle-to-upper left sternal border murmur, with radiation to the right side of the sternum. Additionally, if the shunt is large enough to produce a ratio of pulmonary-to-systemic flow > 2:1, a mid-diastolic murmur (the so-called "diastolic rumble" from extra blood flow across the mitral valve) will also occur at the apex, similar to a long, prominent third heart sound.

If pulmonary hypertension eventually develops, the pulmonic component of the second heart sound will increase in intensity; and on CXR, there will be evidence of cardiac enlargement and increased proximal pulmonary vasculature markings (Image 12-17). The ECG can show LVH initially in large defects, and, eventually, RVH also will develop if the shunt is severe and persistent. If the shunt is small, CXR and ECG are frequently normal. Diagnose using echocardiogram with Doppler.

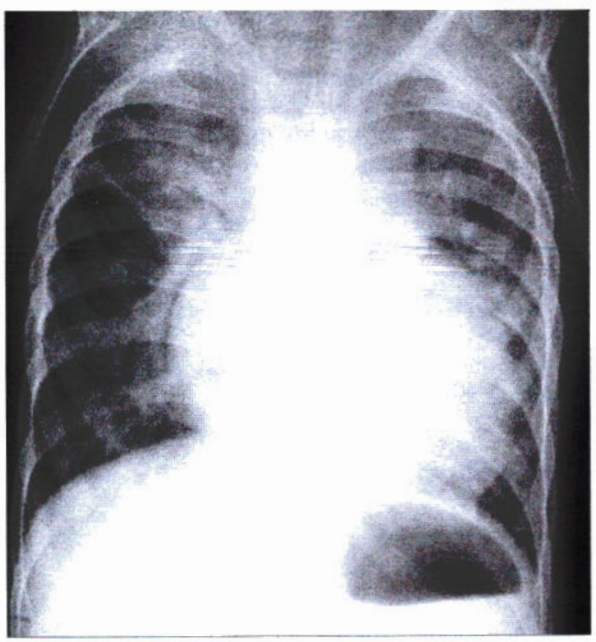

Image 12-17: Large VSD with Pulmonary Hypertension

Most symptoms will occur in term infants 4–8 weeks of age and will consist of volume overload and heart failure. The left-to-right shunt is generally greatest at about age 2 months, when pulmonary vascular resistance has dropped to its lowest level.

You should close persistent shunts that have more than twice the normal pulmonary blood flow. Other management depends on symptoms and time.

Asymptomatic Infants

Initially, if the infant is diagnosed by murmur only and is asymptomatic with a small, quiet heart, do nothing and reevaluate periodically—as usual for "well-child" checks. At 1 year of age, if the murmur is still persistent, refer to a pediatric cardiologist, who may order an echocardiogram. If it is membranous (and thus, with a low likelihood of closing), follow with the cardiologist and proceed to surgery in the patient with an asymptomatic 2:1 persistent shunt (to prevent Eisenmenger's).

Symptomatic Infants

If the infant or child has symptoms/signs of CHF with the VSD, go straight to cardiology consultation. (If a cardiology consult is not available, order an echocardiogram.) If the echo shows an isolated VSD, management depends on the size and type: Surgery for larger membranous defects with elevated, right heart pressures by 6–12 months; for muscular VSDs (or smaller, membranous defects), medical therapy is given a better chance because these are more likely to decrease in size.

Medical therapy may include diuretics, afterload reducers, and/or digoxin.

For the medically treated: If they do not respond adequately (e.g., recurrent CHF, FTT) or there is persisting pulmonary hypertension, especially with trisomy 21, proceed to surgery. Over time, for those on medical therapy, evaluate and look for problems with the family in its ability to cope (can't make appointments, can't keep up with feeds, etc). If these occur in the first year, consider surgery; if not, continue to monitor. At 1 year of age, repeat the echo. If the VSD has become smaller, monitor; if it is not smaller, consider surgery somewhere between 1 and 3 years of age, especially if a 2:1 shunt persists.

Atrial Septal Defects (ASD)

Ostium Secundum Defect

Ostium secundum defects are the most common form of ASD and are located in the mid-septum. These are normally isolated lesions that can be very small to large in

QuickQuiz

- Where do most VSDs occur in children < 1 year of age? > 1 year of age?
- How will "symptomatic" VSDs present?
- What is the therapy for symptomatic VSDs?
- What are the most common ASDs?
- What is the finding of S_2 in an older child with ostium secundum ASD?
- What is the treatment for ostium secundum ASD?
- Which type of ASD requires endocarditis prophylaxis? (Trick question—Don't forget the most recent 2007 guidelines have changed!)
- What are the usual symptoms in an older child with patent foramen ovale?

size. How much left-to-right shunting occurs depends on the size, inflow resistances (ventricular compliances) of the left and right ventricles, and the outflow resistance (vascular bed resistances) of the 2 ventricles. A large shunt results in large increases in flow through the right atrium, right ventricle, and pulmonary artery, compared to normal flow. Cardiac failure is very unusual in infancy. ASDs are twice as common in females as in males.

Older children with ASDs are usually asymptomatic (unless there is pulmonary hypertension from another cause, such as underlying lung disease). On physical examination, S_1 is normal, and S_2 is widely split without respiratory variation.

The ASD itself does not usually produce a very loud murmur—the murmur is from increased flow across the right ventricular outflow tract and pulmonic valve. It is a systolic ejection murmur that is crescendo-decrescendo and heard best at the upper left sternal border. If the shunting is large, an early or mid-diastolic murmur can occur due to increased flow across the tricuspid valve; you can best hear this at the left lower sternal border.

What does the CXR show? Before you answer, think for a moment. What is having increased volumes? That's right! The right atrium, right ventricle, and pulmonary artery—thus, the main pulmonary artery and right heart will be enlarged on CXR, and there is increased pulmonary blood flow.

ECG will show RAD, RVH, and a typical rsR or rSR' pattern in the right precordium. The S wave in the inferior leads also is usually notched.

Echocardiogram is diagnostic.

Pulmonary vascular disease with pulmonary hypertension (i.e., Eisenmenger syndrome) can occur (~ 5%), but usually not until 20–30 years of age. Arrhythmias frequently occur in adults (usually atrial fibrillation/flutter); also, there may be CHF, as well as embolic strokes in adults. This is the reason why surgical (or a catheter device) intervention is usually indicated to prevent these arrhythmias from occurring. Usually, perform closures within the first 5 years to prevent complications. Most defects can be closed with catheter devices.

Ostium secundum defects do not need endocarditis prophylaxis; neither does ostium primum (next), according to the latest guidelines!

Ostium Primum Defect

This defect is located in the lower portion of the atrial septum in the region of the mitral and tricuspid valve rings. This is a form of AV canal defect and is also called a partial AV canal defect. The defect is usually quite large. Usually, the anterior (or septal) mitral valve leaflet is displaced and has a cleft. The tricuspid is usually not involved, but it too can have a cleft in the septal leaflet. According to the 2007 endocarditis prophylaxis guidelines, ostium primum defect no longer requires antibiotic prophylaxis.

Clinically, the left-to-right atrial shunt results in right ventricular hyperactivity, with increased pulmonary blood flow. There are usually a right ventricular outflow murmur, a tricuspid valve mid-diastolic flow murmur, and a widely split S_2. You may hear mitral and tricuspid regurgitation murmurs if the clefts occur in these valves.

The ECG will show left axis deviation (LAD) and right ventricular hypertrophy (RVH), demonstrated by an rsR' pattern in the right precordium. The LAD distinguishes the ostium primum defect from the ostium secundum defect.

Perform early surgical correction in childhood.

Patent Foramen Ovale

This is a normal fetal structure and is present in basically all newborns. Remember: At birth, pulmonary blood flow and venous return increases markedly, and left atrial pressure rises. This functionally closes the foramen ovale. In most instances, anatomic closure occurs by a few years of age. A patent foramen ovale may persist in 10–20% of children > 5 years of age and in adults. Usually, the patent foramen ovale is small and of no clinical significance in childhood. No physical findings or symptoms result. (In adults, closure of a patent foramen ovale may be indicated in cases of TIAs or strokes, if thought to be related to paradoxical emboli due to a right-to-left shunt through the foramen ovale.) There may be an association of patent foramen ovale with migraine headaches.

Complete AV Canal Defect (AV Septal Defect, Endocardial Cushion Defect)

This involves failure of the "central" heart to develop, resulting in a large hole communicating between the atria and ventricles, as well as malformation of the tricuspid and mitral valves. The anterior and posterior segments of each leaflet join each other through the defect (normally, they are separated), resulting in a common AV valve. The AV valve abnormality may result in significant mitral/tricuspid valve regurgitation. The overall result is a large left-to-right shunt and valve regurgitation, leading to a cardiac volume overload and CHF. This is all due to a defect in the development of the endocardial cushions. This is the most common heart defect in Down syndrome (trisomy 21).

The child can present with the characteristic murmur of a VSD, as well as a mid-diastolic rumble that is due to increased pulmonary venous return and increased diastolic flow across the AV valve. A mitral regurgitant murmur (apical pansystolic) may also be present if the cleft in the mitral valve is significant. The same happens if the tricuspid is involved.

These infants most often present with heart failure by 2 months of age. Symptoms can start in early infancy, especially if there is a large left-ventricle-to-right-atrial shunt, or if there is significant valvular dysfunction.

ECG will usually show a left axis deviation and prominent voltages with biventricular hypertrophy. CXR reveals nonspecific, generalized cardiomegaly with increased pulmonary blood flow.

Medical management of CHF can be helpful, but early surgery is necessary, within the first 6–12 months, to prevent pulmonary vascular disease (Eisenmenger syndrome). Usually, the best outcomes occur in those with balanced defects and similar-sized ventricles (occasionally 1 ventricle can be small/hypoplastic). Children with Down syndrome usually have a good chance of having a compatible anatomy for correction.

L-transposition of the Great Arteries (Ventricular Inversion or Congenitally Corrected TGV)

L-transposition occurs when the embryonic cardiac tube loops to the left instead of the right. The anatomic left ventricle ends up on the right side and connects the right atrium to the pulmonary artery. The anatomic right ventricle is now on the left side and receives oxygenated blood from the left atrium through a tricuspid valve, while the right ventricle ejects the blood to an anteriorly placed left-sided aorta.

Confusing, huh? There is transposition of the great arteries (the aorta comes off the anatomic RV and the pulmonary artery) and "inversion" of the ventricles, but this allows normal flow of venous blood to the lungs and oxygenated blood to the rest of the body. Thus, this is known as "corrected" transposition. Just about all neonates with this lesion have a VSD or pulmonic stenosis. Many have conduction defects, and complete heart block develops at a rate of about 1–2% per year.

The ECG will usually show Q waves in the right chest leads and no Q waves on the left—indicating that activation of the septum occurs from right to left. CXR will show the transposed aorta as a "straight shoulder" on the left heart border.

If patients are doing well, surgery may not be indicated because it can be technically difficult and increases the risk of conduction defects. If there is significant hemodynamic load and the patient is symptomatic, perform repair with VSD closure and relief of pulmonic stenosis (PS). In higher risk situations, palliation can be done; and the pulmonary artery may be banded in the case of a large, left-to-right shunt, or an aortopulmonary shunt can alleviate hypoxia when there is more severe PS. A pacemaker may eventually be needed if AV block develops.

Sinus of Valsalva Fistula

Rupture of a sinus of Valsalva into a cardiac chamber is usually due to a structural abnormality in the sinus and is uncommon. The most common fistula involves the anterior (right coronary) aortic valve sinus, which ruptures into the right ventricle or right atrium. The other, less commonly seen fistula occurs from the noncoronary or left coronary sinus into the left atrium or left ventricle.

An associated VSD may increase risk of rupture.

Rupture is usually associated with acute chest pain and dyspnea, with sudden onset of murmur and congestive heart failure. Echocardiogram is the best diagnostic tool. Surgical closure is necessary.

REGURGITANT LESIONS

Aortic Regurgitation

Aortic regurgitation (AR) presents with a high-pitched, early diastolic murmur that begins with the aortic component of the second heart sound. An aortic systolic ejection murmur may also be present due to increased flow across the valve or to a structural abnormality of the valve itself. Also be on the lookout on the Board exam for an Austin Flint murmur associated with rheumatic fever. Austin Flint is a low-pitched, mid-diastolic murmur at the apex and is due to the regurgitant aortic jet striking the anterior leaflet of the mitral valve, preventing it from opening fully, thus causing relative "mitral stenosis."

Most kids are asymptomatic unless it is more severe; then they'll present with fatigue or exercise intolerance. Chronic or acute AR can present with CHF.

Pulse pressure is widened—the systolic pressure is elevated due to increased LV stroke volume, and diastolic pressure is reduced because of "runoff" into the LV and peripheral vascular dilatation.

Quick Quiz

- What is the "defect" in complete AV canal defect?
- What is the most common heart defect seen in trisomy 21?
- By what age will heart failure occur in most children with complete AV canal defects?
- What is L-transposition of the great arteries?
- Describe the murmur of aortic regurgitation.
- What are some causes of aortic regurgitation in children?
- Worldwide, what is the most common cause of mitral regurgitation? In the U.S. proper?
- Describe mitral valve prolapse. Which diseases carry an increased risk of having MVP?

Some causes of AR in children:

- Congenital aortic stenosis usually occurs due to a bicuspid aortic valve; over time, insufficiency can develop. You usually treat AS with valvulotomy or valvuloplasty—either of which will increase the amount of AR, but usually, the degree of AR won't be clinically significant.
- Marfan syndrome is associated with dilated sinuses of Valsalva and ascending aorta. AR can result and be severe.
- Rheumatic fever is probably the # 1 cause worldwide but is less common in the U.S.
- Infective endocarditis, especially that due to *S. aureus*.

You can monitor most patients for signs/symptoms with periodic ECGs, and echocardiograms for those with significant AR. Use afterload reduction (ACE inhibitors, hydralazine) with moderate or severe AR to lessen the volume and reduce the amount of regurgitant flow. Do surgery if the patient is symptomatic, if there are signs of LV dysfunction or severe dilation, or if acute regurgitation has occurred with resultant heart failure.

Mitral Regurgitation

Mitral regurgitation (MR) presents with an apical, high-pitched blowing systolic murmur. It can radiate to the left axilla and the back. The murmur usually starts at the first heart sound and is holosystolic in character. With mitral valve prolapse, the murmur will usually start later (mid-to-late systolic, following the "click").

Worldwide, the most common cause of mitral regurgitation is rheumatic fever; in the U.S., it is mitral valve prolapse, which occurs in about 1–5% of the population. Mitral regurgitation can also occur if there is a cleft in the anterior leaflet of the mitral valve, or if papillary muscle dysfunction has occurred (cardiomyopathies).

Many patients require no therapy, but in those who are symptomatic, you can use afterload reduction to postpone surgery. For those who worsen, or in whom LV function is deteriorating, perform valvuloplasty or valve replacement.

Mitral Valve Prolapse

In mitral valve prolapse (MVP), the posterior (or the anterior) leaflet of the mitral valve prolapses back into the left atrium. Most of the time, there is no explanation for why this is happening. MVP occurs more frequently in those with Marfan's (they have elongated chordae tendineae), Ehlers-Danlos syndrome, or the mucopolysaccharidoses. The extent of prolapse depends mostly on an inverse relationship with LV volume; i.e., if volume is increased (like when the patient lies down), then the prolapse will decrease.

Patients with MVP usually have a mid- to late-systolic crescendo murmur at the apex—almost always preceded by a click. If you have the patient sit or stand (decrease LV volume), the murmur will get louder and longer, and when he/she squats or lies down, the murmur becomes softer, shorter, and later in systole. The Boards like you to think of the position changes with MVP—e.g., a murmur only heard with standing. Most patients are asymptomatic, but some will have chest pain and/or palpitations. Studies show these are not associated with MVP in pediatric patients. Arrhythmias may also occur.

(Note: On the other hand, if they describe an increased early systolic ejection murmur with standing, think hypertrophic cardiomyopathy!)

Pulmonary Regurgitation

The murmur of pulmonary regurgitation is an early, low-pitched, decrescendo diastolic murmur that starts with the pulmonary component of the second heart sound. It can become high-pitched if pulmonary artery diastolic pressure is increased, such as with pulmonary hypertension. The regurgitation is usually not a clinical problem because of the lower pulmonary pressures. If the regurgitant volume is 2x normal, a soft, pulmonary systolic ejection murmur may develop, and the second heart sound may widen but is not fixed.

The most common cause of pulmonary regurgitation is as a result from surgery for pulmonary stenosis or for tetralogy of Fallot. Congenital pulmonary regurgitation is rare.

Manage most patients who develop pulmonary regurgitation after valvuloplasty or valvular surgery on a stenotic valve, with periodic follow-up. Most do not require any special therapy. If symptoms become worse, or RV function is compromised, seriously consider valve replacement. This may be an increasingly seen problem in postoperative tetralogy of Fallot.

Tricuspid Regurgitation

The murmur of tricuspid regurgitation is a pansystolic murmur that is loudest along the lower left sternal border, with radiation to the right. You may also hear a low-pitched, mid-diastolic murmur in the tricuspid area. The CXR may show a right lower cardiac border that is large, and the ECG may also show right atrial enlargement. If the right atrium is very enlarged, you may see distended jugular veins or an enlarged liver. Trace or mild tricuspid regurgitation is usually well tolerated and is common. Pretty much anything that dilates the right ventricle and increases pressure/volume will result in some tricuspid regurgitation. Rare causes include endocarditis (suspect this in an adolescent who is injecting IV drugs), pulmonary hypertension, Ebstein anomaly, and carcinoid syndrome.

OBSTRUCTIVE LESIONS

Pulmonic Stenosis (PS)

Pulmonic stenosis is the 2nd most common of the congenital cardiac defects. Again, VSD is the most common. Usually, PS is due to abnormalities of the valve leaflets. RVH occurs because of the valve obstruction. The overall formation and size of the right ventricle and tricuspid valve are related to the time in gestation at which pulmonic stenosis occurs. If it is early, venous return is likely to be diverted across the foramen ovale and results in a relatively small RV and tricuspid valve, with eventual pulmonary atresia. If the stenosis occurs later in gestation, RV formation is likely to be normal.

After birth, presentation depends on the extent of the stenosis and to the degree that RV and tricuspid valve development have been affected. In critical pulmonic stenosis, the RV cannot eject the total systemic venous return; and thus, pulmonary blood flow from the pulmonic valve is markedly diminished. There is right-to-left atrial shunting (usually through a patent foramen ovale or as ASD) away from the thickened, noncompliant, right ventricle, and cyanosis will be present. These infants will appear as though they have complete pulmonic atresia, and most of the pulmonary blood flow will have to come from the aorta to the pulmonary artery through a patent ductus arteriosus. Clinically, infants with severe pulmonic stenosis present in early infancy with severe cyanosis and cardiac collapse as the ductus closes (critical pulmonary stenosis is an indication for prostaglandin-E [PGE_1] therapy to maintain a patent ductus arteriosus and sufficient pulmonary blood flow).

In those with more moderate pulmonic stenosis, mild cyanosis may develop if the foramen ovale remains open, but the cyanosis disappears if, and/or when, the foramen ovale closes or the RV obstruction is relieved. In general, isolated PS is not a cyanotic lesion except when critical in the newborn.

For the great majority of affected children with pulmonary stenosis, no symptoms occur. They are picked up only because of the heart murmur. A systolic ejection click (that varies with respiration) along the left sternum is followed by a crescendo-decrescendo murmur. You can hear this murmur best at the left upper sternal border, and it radiates to below the left clavicle and often to the back.

ECG may show peaked P waves (lead II) indicating the RA enlargement, as well as RAD and RV hypertrophy. CXR will show RV prominence and prominent main pulmonary artery with normal pulmonary blood flow.

Over time, some children, even with moderate stenosis, will have little or no worsening or increase in RV systolic pressure—probably due to the fact that the valve opening has enlarged with growth. Other children, however, will have a marked increase in RV pressures, leading to high RV end-diastolic pressures and rarely right heart failure.

Children with mild stenosis require no treatment and no longer require endocarditis prophylaxis. Patients with more moderate (RV pressure over 50% of systemic)-to-severe (RV pressure greater than systemic) stenosis will develop problems over time and should have pulmonary balloon valvuloplasty or surgical valvotomy. Additionally, treat other children who are symptomatic with exercise symptoms and those with significant RV hypertrophy. Finally, consider treatment for any child with a RV systolic pressure > 50 mmHg or 50% of systemic pressure.

To estimate RV pressure, cardiologists often use the tricuspid regurgitant jet. The peak velocity (e.g., 4 m/s) can be used to calculate a gradient from the right atrium to the right ventricle using the modified Bernoulli equation (gradient = $4v^2$). If you assume a normal RA pressure of 5 mmHg, then the RV pressure = gradient + 5 mmHg (e.g., gradient = $4(4^2$ m/s) = 64 mmHg (gradient) + 5 mmHg (RA) = 69 mmHg RV pressure). They may not expect you to make the calculation, but instead may give you an echo report with a tricuspid regurgitant jet echo–Doppler gradient of X mmHg. (Normal right ventricular pressure is ~ 25 mmHg.)

(Alagille syndrome [more in the Genetics section] seems to be popular on the Boards lately. It is associated with pulmonary valvular or peripheral stenosis. Noonan syndrome is also associated with pulmonic stenosis.)

Peripheral Branch Stenosis

In many infants up to 6–12 months of age, a "physiologic" branch pulmonary artery stenosis occurs and produces an innocent murmur—usually grade 1–2/6 radiating to both axilla and all lung fields. It resolves with growth. It can also occur and be severe/pathologic in infants with congenital rubella syndrome, Williams syndrome, or Alagille syndrome (arteriohepatic dysplasia).

QuickQuiz

- What is the 2nd most common congenital cardiac lesion?
- An infant suddenly becomes cyanotic, with signs of cardiac collapse when the ductus arteriosus closes. What is a possible explanation?
- True or false? Most children with pulmonic stenosis are asymptomatic.
- Describe the murmur of pulmonic stenosis.
- Does pulmonic stenosis warrant endocarditis prophylaxis?
- True or false? In congenital aortic stenosis, most of the valves are monocusp.
- How will an infant present with severe aortic stenosis?
- What is the murmur of an older child with aortic stenosis?
- True or false? Clinical findings are helpful in discerning the extent of aortic stenosis that is occurring.
- A child with known aortic stenosis presents with new-onset syncope. What should you do next?

Aortic Valve Stenosis

Almost all (> 85%) congenital stenotic aortic valves are bicuspid—1 cusp is small and 1 is large. The opening is described as "fish-mouth" in character. The remaining 15% have only 1 cusp—a monocusp—and its opening is described as being like a "teardrop." If there is severe aortic stenosis at birth and the foramen ovale closes, left atrial pressure will rise while LV output is maintained. This will result, however, in pulmonary edema as left atrial pressure continues to rise. If the foramen is open and a large left-to-right shunt occurs, cardiac output will be decreased, but the pulmonary edema will be less. Either way, if the foramen is open or closed, LV function will eventually deteriorate and LV failure will occur. If the aortic stenosis (AS) is not that severe, most infants are able to maintain an adequate cardiac output by developing LV hypertrophy to overcome the obstruction. Unfortunately, congenital AS is often progressive. As the infant/child grows, the valve opening becomes smaller and smaller, and stenosis becomes more pronounced.

Clinically, the infant with severe, congenital AS will present fairly quickly with a systolic murmur at the right or left upper sternal border, with an early ejection click. The infant's perfusion and pulses will be diminished, and he/she can have the appearance of being in septic shock. CXR will usually show marked cardiomegaly with severe pulmonary edema. Echo is diagnostic.

In older children, the murmur (a crescendo-decrescendo, harsh-to-rough systolic murmur with suprasternal notch thrill) will be significant, and the other clinical findings generally correlate with the degree of stenosis. You usually best hear the murmur at the right upper sternal border, and it radiates into the suprasternal notch and neck. An apical ejection click that does not vary with respiration is heard commonly. Children do not usually develop the diminished pulse volume, as seen in adults. It takes much longer for the LV volume to be ejected, so the aortic component of the second heart sound is delayed, frequently resulting in narrowing or loss of the split heard with the second heart sound. It is rarer in children, but, occasionally, the aortic component will occur after the pulmonic component, known as paradoxical splitting. On inspiration, the second heart sound's gap will narrow, and, on expiration, the gap will widen. You usually will hear a third heart sound at the apex.

Note: Physical findings, CXR, and ECG are not reliable in predicting the severity of the AS! Therefore, you must periodically assess the pressure gradient between the LV and aorta, as well as the hemodynamic status, using either Doppler echocardiogram or cardiac catheterization. You may do exercise stress testing to assess adequacy of myocardial perfusion. Usually, if Doppler indicates severe AS, or symptoms occur, consider cardiac catheterization to assess more accurately the gradient and valve competency.

If, on the Board exam, you're presented a child with known AS and the child has syncope or chest pain, look for cardiac catheterization as an answer. Generally, a Doppler gradient of 70 mmHg correlates with > 50 mmHg peak-to-peak gradient with direct catheterization, indicating the need for therapy. Usually, this means that valve surface area has fallen to < 0.65 cm^2/m^2 (normal is > 2 cm^2/m^2). Balloon valvoplasty is now the treatment of choice in children. Usually, patients do well initially and for many years. Eventually, however, stenosis recurs, and ~ 40% require repeat treatment (including surgery) within 10 years.

When the aortic stenosis is severe, all patients will eventually require surgery, with either the Ross procedure or mechanical valve replacement. The Ross procedure consists of moving the pulmonary valve ring, with the valve intact, into the aortic annulus, and placing a homograft aortic valve into the right ventricular outflow tract. Anticoagulation is not required, and there is a very low risk of restenosis. Unfortunately, the new pulmonary valve (the aortic homograft placed between the RV and PA) does not grow and often becomes stenotic and/or insufficient over time. It requires surgical replacement in 10–15 years. If possible, defer either the Ross or mechanical valve replacement until the child is fully grown to alleviate future surgeries related to the child's growth.

Hypertrophic Cardiomyopathy (HCM), Hypertrophic Obstructive Cardiomyopathy (HOCM), or Idiopathic Hypertrophic Subaortic Stenosis (IHSS)

HCM is transmitted as an autosomal dominant (AD) disorder with variable expression. About 50% of the mutations occur on chromosome 14. (Some think of HOCM/IHSS as a subtype of HCM. Eventually all with HCM die from arrhythmias but only about 25% will have obstruction—thus HOCM/IHSS.) A systolic murmur is often present. It is not associated with systolic clicks, like AS, and there is not a suprasternal notch thrill. The murmur is delayed in onset—a grade 3–4/6 crescendo-decrescendo systolic murmur at the middle left to right upper sternal border. A thrill is palpable over the precordium in some patients (but again, not the suprasternal notch). Gallops (third and fourth heart sounds) are common. The murmur gets louder with Valsalva or rising to an erect position. Either of these reduces venous return, resulting in a decrease in LV volume and an increase in the effect of the obstruction. If you have the child squat, venous return will increase and decrease the murmur due to LV dilatation. Note: These same maneuvers in AS will produce the opposite effects. (This can be your clue to make this diagnosis: Look for a child in whom the murmur gets Softer with Squatting. It will be HOM/IHSS, not AS!)

The CXR will show LVH without an enlarged ascending aorta. The ECG is abnormal in most cases, revealing LVH, prominent septal Q waves, and abnormal repolarization or strain (look for negative T waves in V6). Echocardiogram is diagnostic. Genetic testing is now available to assist in the diagnosis of borderline cases or to assist in the screening of family members of the proband.

Children with HCM are at risk to die from arrhythmias. You can try treatment with beta-blockers, but this is only a temporary measure to reduce obstruction. Calcium channel blockers are useful if the child has diastolic dysfunction. Amiodarone is the only drug shown to improve mortality in HCM, but it has long term use complications (see prior section). Some children require surgical resection (or alcohol ablation) of the hypertrophied cardiac muscle or implantable defibrillators. Another clue: HCM (with or without obstruction) is the most common cause of sudden death in athletes at sporting events in the U.S.

Supravalvular Aortic Stenosis

This condition is narrowing that occurs just above the level of the coronary arteries. The coronaries arise just proximal to the obstruction and often have thickened medial and intimal layers, with occasional fibrous tissue that compromises coronary blood flow. You can have isolated supravalvular AS, but it is most commonly associated with Williams syndrome (which is the result of a defect in elastin). Remember that Williams syndrome involves mental retardation, "cocktail-party personality," elf-like facies, and narrowing of the peripheral systemic and pulmonary arteries (also remember they can have systemic hypertension related to renal artery stenosis). When listening to the heart, you'll frequently hear a systolic murmur (without click) at the base and toward the neck. With supravalvular aortic stenosis, the jet directed into the innominate artery usually results in a blood pressure 15 mmHg higher in the right arm, compared to the left arm (so-called Coanda effect). Do an echo and Doppler study to quantify the severity of the supravalvular obstruction; occasionally, cardiac catheterization will be required as well. If obstruction is severe, surgery is indicated.

Aortic Hypoplasia and Interruption

Hypoplasia of the aortic arch most commonly occurs in the aortic isthmus (the part of the aorta between the origin of the left subclavian and the ductus attachment). The most severe form, obviously, is complete interruption (and most commonly occurs proximal to the left subclavian); this is almost always associated with multiple congenital and cardiac defects (VSD, aortic/subaortic stenosis, mitral abnormalities).

In cases of true interruption of the aortic arch, remember to consider a FISH test (22q11 marker) to rule out DiGeorge syndrome. If complete interruption has occurred, distal aortic blood flow is provided only by right-to-left flow through a patent ductus arteriosus. Initially, when the ductus arteriosus is dilated, there may be no difference in blood pressure between the upper and lower body, but there might be differential cyanosis between the feet and hands. Over time, however, the ductus arteriosus constricts so that flow to the lower part of the body is diminished and compromised. The LV becomes overloaded as well, and kidney and other organ function in the lower part of the body is adversely affected.

In infants, look for a clinical presentation of poor systemic output with CHF, decreased lower extremity pulses, and differential cyanosis (pink above/blue below). Echocardiogram will usually show the abnormality, but cardiac catheterization may be necessary to fully elucidate the problem.

Those infants with just narrowing of the transverse arch may respond to inotropes and diuretics. With severe arch narrowing or interruption, prostaglandin E_1 (PGE_1) is extremely useful in dilating the ductus arteriosus and returning adequate flow to the lower body. This will allow the infant to stabilize for surgery.

Coarctation of the Aorta (Adult-Type Postductal and Infantile-Type Preductal)

This obstructive lesion usually presents in otherwise asymptomatic older children and young adults during

Quick Quiz

- How may HCM be inherited?
- How can you differentiate between IHSS and aortic stenosis?
- An athlete suddenly collapses on the basketball court. What is the most likely etiology?
- What syndrome is supravalvular aortic stenosis associated with?
- How will infants with significant coarctation of the aorta present? Older children?
- What is the classic x-ray finding in a 7-year-old with undiagnosed coarctation of the aorta?
- What is the best therapy for coarctation of the aorta?

a workup of hypertension or murmur. If the obstruction is severe, it can present as CHF or cardiogenic shock in newborns.

The ductus arteriosus is wide during fetal development. Coarctation develops from a defect in the vessel media, causing a posterior infolding ("posterior shelf") of the vessel. The narrowest part is juxtaductal; therefore, coarctation is unlikely to produce significant alteration in the distribution of blood flow. After birth, the ductus constricts on the pulmonary end first, so that an aortic opening is still present—often for days. However, if the aortic end of the ductus constricts, blood flow will become obstructed.

Clinically, in infancy, severe coarctation looks a lot like severe aortic stenosis, with "septic shock" appearance. If left ventricular function can be restored (usually with inotropes), you will see the classic pressure difference between the upper and lower body. Murmurs are not common, but if the ductus is patent, you may hear a continuous murmur along the left sternal border or mid back. Surgically excise the coarctation after stabilization in infants with rapid decompensation. For many infants up to 3–4 weeks of age, prostaglandin E_1 is the best stabilizing therapy because it may open up the ductus enough to relieve the acute aortic obstruction.

In those with a small aortic shelf, or slow occlusion of the aortic side of the ductus, aortic obstruction develops slowly over weeks to months. These infants are more likely to develop collaterals and have less chance for acute events. However, heart failure still may occur at 3–6 months of age because the coarctation becomes more severe. If the child has not had heart failure by 6 months of age, it is unlikely to develop before adulthood. In young children beyond 6 months of age, it may present with hypertension or murmur. Epistaxis, claudication-like symptoms in the lower extremities with exercise, and headaches are described but are uncommon. Stroke is rare < 7 years of age, but, if it occurs, it is likely associated with a ruptured berry aneurysm. According to the latest guidelines, antibiotic prophylaxis is not recommended anymore.

What about older children and adolescents? How do they present? Diagnose from pulses and blood pressures—not murmurs. Pulses in the upper extremity are strong with associated hypertension, while the femoral pulses are weak and delayed compared with the radial pulse. Other abnormalities can occur, including an aberrant right subclavian artery below the coarctation, which would result in the right arm's blood pressure/pulse being lower than the left arm's. A murmur may be present posteriorly at the left scapular angle; and often there are murmurs/clicks from associated aortic stenosis or bicuspid aortic valve (the latter are highly associated). You may hear continuous murmurs over the collateral vessels.

CXR has some features you need to know! Look down the left upper border of the aortic arch and descending aorta. The area of dilatation below the coarctation and the dilated aortic segment just above the coarctation can sometimes look like the "3" sign. Rib notching is classic, but may not develop for 5–6 years. It occurs at the lower margins of the ribs, at about the middle 3rd, and is due to erosion of the bone by large intercostal arteries. It occurs in > 50% of affected older children. Do an echocardiogram first; MRI is also helpful in diagnosis.

Untreated coarctation has several potential complications: Hypertension, rupture of a berry aneurysm, CHF, endocarditis, and rupture of the aorta (reported only in adults). Surgery is the traditional treatment of choice—usually excision with direct anastomosis. Balloon angioplasty has become the treatment of choice for re-coarctation and, can be used for native coarctation.

Mitral Valve Stenosis

Congenital mitral stenosis is uncommon, usually severe, and presents early in infancy. It is most often associated with other left heart obstructions or hypoplasia (part of Shone complex). The baby will present with pulmonary edema; CHF also is possible. The pulmonic component of the second heart sound is usually loud. Normally, you hear an apical diastolic murmur, but usually not an opening snap in infancy because the valve is so thick and immobile. Mitral insufficiency may occur with the stenosis, so you may also hear an apical systolic murmur. ECG may show broad-notched P waves, indicative of the left atrial enlargement, but RVH is seen instead of LVH due to the pulmonary hypertension, which is common.

Unfortunately, medical management of severe congenital mitral stenosis with CHF in infancy is rarely successful. A prosthetic valve is sometimes indicated, but it must be replaced as growth occurs. Additionally, you must give anticoagulation to prevent thrombus

formation on the valve. Infants and children may do okay with dilatation of the stenotic valve with a balloon catheter, thus deferring valve surgery of replacement until a later date.

Tricuspid Stenosis

Isolated, tricuspid stenosis is very rare and usually is associated with a more global problem, like complete underdevelopment of the right ventricle. Right atrial enlargement is common, and this frequently manifests on ECG with a large peaked P wave.

RIGHT-TO-LEFT SHUNTS

Tetralogy of Fallot

This is the most common cyanotic heart lesion in children with congenital heart disease who have survived untreated beyond infancy. It makes up 7–10% of congenital defects.

4 things make up the tetralogy:

1) RV outflow tract obstruction (subpulmonary valve stenosis)
2) VSD (malalignment)
3) Overriding aorta (dextropositioning)
4) RVH

Why is the child cyanotic? Because he/she has a right-to-left shunt as a result of pulmonary outflow tract obstruction, which causes various amounts of systemic venous blood to be shunted across the VSD into the aorta. These children tend to develop "tet" spells or "blue" spells, which occur when there is an acute reduction in pulmonary blood flow, a drop in systemic afterload, and worsened right-to-left shunt. The attacks may last only a short while and not have any sequelae, or they can be prolonged and produce limpness, exhaustion, or collapse. In rare instances, the attacks can cause seizures or death. Fortunately, most of these children have corrective surgery by 6–12 months of age, so relatively few today have hypoxic spells.

A classic question to look for on the Boards relates to the cyanotic child who squats after exertion. This causes increased arterial oxygen saturation and is probably due to increased systemic arterial resistance (and therefore increased pulmonary blood flow). Again, these children are rarely seen anymore today (except on Boards) because of corrective surgery done more consistently at an early age. If, for some reason, the child has not had surgery, he/she is at risk for brain abscess, cerebral thrombosis with hemiplegia, and infective endocarditis.

The murmur in an untreated child is due to the right ventricular outflow obstruction. You can hear a systolic murmur best at the middle or left lower sternal border. There may be an associated aortic click in older patients due to aortic dilation. As the RV outflow obstruction becomes severe during a "tet spell," there may be very little flow across the RV outflow tract and the murmur may disappear.

CXR classically shows the "boot-shaped" heart or "coeur en sabot" (Image 12-18). 25–30% have a right aortic arch. ECG will show RAD and RVH. Echocardiogram is diagnostic, and cardiac catheterization is often not indicated.

There is a subgroup known as "acyanotic Fallot." These children have minimal RV outflow obstruction and therefore do not have a significant right-to-left shunt.

Treatment [Know]: PGE_1 is helpful in the neonate with pulmonary outflow obstruction to alleviate cyanosis. Usually, you will perform corrective surgery by 6–12 months of age, but sometimes earlier. If a hypercyanotic "tet" episode occurs before surgery, treat by placing the infant on its abdomen in a knee-chest position or by holding the infant with its knees flexed on the abdomen. You can try oxygen; but it is usually not that helpful because the lungs are not receiving much blood to oxygenate. Sedate with morphine (0.1–0.2 mg/kg IV or SubQ) to relieve a protracted episode. IV beta-blockers can also be helpful.

Avoid factors that worsen agitation. You can use vasopressors, particularly phenylephrine, to raise systemic resistance and increase pulmonary blood flow. Iron deficiency anemia can set these spells off, so cyanotic infants should have hematocrits of 50–55%. The hematocrit should not exceed this value, however, because this increases risk for cerebral thrombosis. If surgery cannot be performed, give propranolol 0.5–1 mg/kg/dose orally 2–4 times daily to prevent attacks.

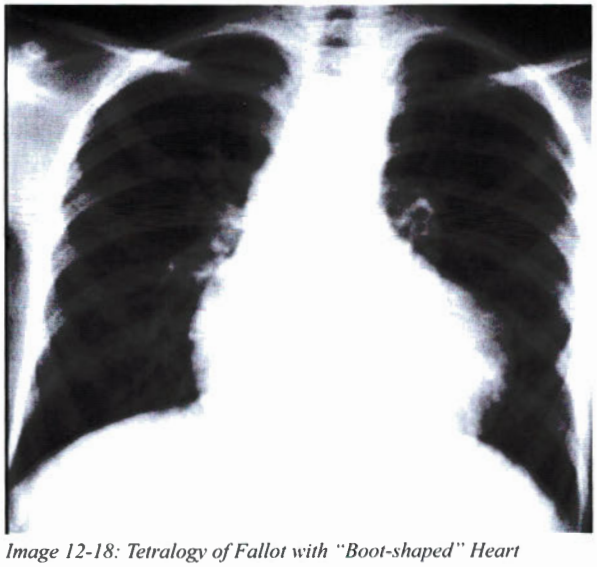

Image 12-18: Tetralogy of Fallot with "Boot-shaped" Heart

QuickQuiz

- What is the most common cyanotic heart lesion associated with congenital heart disease of infants who survive past infancy?
- Name the 4 components of tetralogy of Fallot.
- A cyanotic child who squats after exertion probably has what cardiac abnormality?
- A child with undiagnosed tetralogy of Fallot is at risk for what brain infection?
- What is the classic x-ray finding in tetralogy of Fallot?
- A child with tetralogy of Fallot has a prolonged, severe "tet" spell. What can you use to relieve the symptoms?
- What is the most common congenital anomaly presenting with cyanosis in the first few days of life?
- Describe the anatomy of complete transposition of the great vessels.
- What is the classic x-ray finding in complete transposition of the great vessels?

What happens in surgery? Close the VSD, resect the infundibular subpulmonic muscle, and, sometimes, place RV outflow and main pulmonary artery patch to enhance the flow of the outflow tract. Pulmonary valvulotomy is also sometimes done. Survival rates are ~ 95% for those with uncomplicated Fallot. About 10–15% require further surgeries for recurring pulmonary stenosis or long-term significant insufficiency. Complications are rare, but the most common is post-op ventricular arrhythmias (< 1%). The Boards want you to remember ventricular arrhythmias in post-op tetralogy of Fallot with residual PS or severe PI.

Complete (d-) Transposition of the Great Arteries

Complete transposition of the great arteries is the most common cardiac cause of cyanosis in the newborn during the first few days of life. (Remember: Tetralogy of Fallot is the most common for all ages together.) It comprises 4–6% of congenital defects. What happens here? The systemic venous return goes into the right atrium and the right ventricle and is then ejected out into the "transposed" aorta that is coming off of the RV. Meanwhile, the oxygen-rich pulmonary venous return is going into the LA and LV and is ejected back into the lungs via the "transposed" pulmonary artery.

So we have 2 ("parallel") different circulations—2 different circuits that must somehow connect or the infant dies quickly. In ~ 50% of cases, the connection is only through a patent foramen ovale and, more rarely, a secundum ASD. If neither allows much oxygenated blood to mix, there will be severe cyanosis at birth. VSDs may allow more mixing, so less cyanosis occurs. The ductus arteriosus is open early, but it closes very quickly after birth and doesn't help very much.

The infant with transposition but without a VSD usually presents in the first few hours after birth. The only initial presenting sign/symptom in an otherwise healthy-appearing baby may be severe cyanosis. If there is ductal right-to-left shunting, reversed differential cyanosis (blue above and pink below) may be seen. Initial CXR and ECG are frequently normal.

Physical exam will show a single, loud second heart sound (because the aorta is right under the sternum). There can be a 2–3/6, nonspecific, systolic ejection murmur at the middle left sternal border. The infant who has a large associated VSD can develop CHF and modest cyanosis by 3–4 weeks of age. These infants usually have tachypnea and dyspnea.

ECG may be helpful after ~ 5 days, with a persistently positive T wave in the right precordium (lead V1). CXR can vary from normal to the classic findings—egg-shaped or oval-shaped heart with a narrow mediastinum and small thymus. You usually see this classic finding, though, in only ~ 33% of affected infants. Echocardiogram is diagnostic.

Balloon atrial septostomy to create an atrial septal defect offers immediate palliation and is sometimes done in conjunction with cardiac catheterization—but you can do it under echo guidance right in the nursery. The use of PGE_1 infusion can be helpful. The increased pulmonary flow is across the PDA and increases venous return to the LA, enhancing atrial mixing.

Perform arterial switch surgery, the treatment of choice, once the infant is stabilized. It should be done before 2–3 weeks of age, before the LV can regress into an RV-like ventricle because of the low pressures it faces. Operative survival is 90–95%.

Double Outlet RV (Including Taussig-Bing Anomaly)

This is a rare group of disorders in which both the aortic and pulmonary valves are positioned over the RV, and the only outflow from the LV is through a VSD. Different scenarios can occur with variable cyanosis, depending on VSD location and degree of associated PS. The RV can supply the pulmonary artery, and the aorta overrides the VSD, with subpulmonic stenosis also occurring. This results in a "tetralogy of Fallot-like" lesion. At times, the aorta can come off of the RV, and the pulmonary orifice is supplied by the overriding VSD with little LV flow to the aorta (Taussig-Bing anomaly). This acts more like a transposition of the great arteries with severe cyanosis. Coarctation is also found in ~ 25% of these patients. Surgical correction is the treatment option.

Tricuspid Atresia

Tricuspid atresia is fairly common. ~ 1% of all congenital heart disease is due to tricuspid atresia. The tricuspid opening does not exist, meaning that the only way of getting blood from the right atrium to the rest of the circulation is via a foramen ovale or ASD. Here, the systemic and the pulmonary venous return mix.

Usually, there is a VSD. Pulmonary blood flow is across the VSD, through the hypoplastic RV, and into the PA. If there is severe PS or a small VSD, a PDA may be necessary to supply adequate flow and oxygenation. Cyanosis appears within hours to days after birth, when the ductus begins to close. Cyanosis is the key presenting sign. There is often a VSD or PS murmur.

CXR varies depending on the size of the VSD and degree of PS. Small VSD and/or severe PS will show diminished pulmonary vasculature and small heart with a round or "apple-like" shape; large VSD and/or mild PS will show increased pulmonary markings and large heart.

ECG will show left superior axis deviation (0° to –60°) and LVH with decreased RV forces for an infant. This is helpful since the other 2 common cyanotic diseases, tetralogy and complete transposition, have RAD and RVH. [Know for the Boards!] Review: What are the congenital heart defects with left axis deviation? Ostium primum ASD, complete AV canal, and tricuspid atresia.

Treat surgically on an emergent basis if there is significant cyanosis. Do a palliative systemic-pulmonary shunt (modified Blalock-Taussig anastomosis or central anastomosis) in newborns or young infants. In older infants, replace the shunt by a cavopulmonary connection between the superior vena cava and the right pulmonary artery (called a Glenn shunt). In later years, perform the modified Fontan procedure. This diverts the inferior vena cava to the pulmonary arteries. This final procedure leads to all systemic venous return (except that from the coronary sinus) flowing into the lungs and allows the single functioning ventricle to maintain systemic output. The patient is no longer cyanotic.

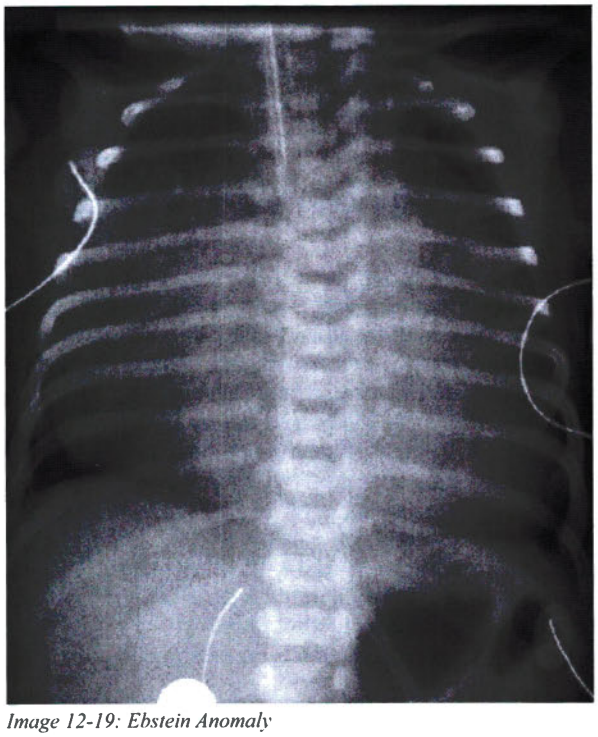

Image 12-19: Ebstein Anomaly

Ebstein Anomaly

Ebstein anomaly (EA) is rare—except on Board exams! Here, the posterior and septal leaflets of the tricuspid valve are displaced downward and attached to the RV wall. This displacement divides the RV into 2 sections—a proximal, "atrial-like" segment and the distal, "ventricular-like" segment. The atrial-like segment and the RA are usually huge, and tricuspid regurgitation is significant. Look for a huge RA on ECG and x-ray (Image 12-19).

Most EA patients are cyanotic soon after birth due to atrial right-to-left shunt, but this resolves until later childhood or young adulthood. On the Board exam, look for the use of maternal lithium and development of Ebstein's! Exercise tolerance gradually deteriorates during childhood. Paroxysmal supraventricular tachycardia is common. The ECG may show an RBBB or WPW pattern.

Treat CHF that is not severe with digitalis and diuretics. Surgical therapy, with tricuspid valvuloplasty or replacement, may be required at any time. Life expectancy varies widely, depending on the severity and specific conditions of each individual. Usually, however, the cause of death is CHF or arrhythmia.

Pulmonary Atresia with Intact Ventricular Septum

Pulmonary atresia occurs in about 1–2% of infants with congenital heart disease during the first year of life. Most have a hypoplastic and thick-walled RV with a very underdeveloped tricuspid opening and valve. Systemic venous return to the lungs occurs across the atrial septum to the left heart and aorta. The pulmonary circulation is usually maintained through a PDA.

Cyanosis is common early, but affected infants deteriorate and die unless they are given PGE_1 to keep the ductus arteriosus open. Perform an ECG because, in pulmonary atresia, you see an inferior QRS axis (0° to 90°) with LVH, while in tricuspid atresia, you see superior QRS axis with LVH.

Consider cardiac catheterization in this lesion for prognosis and therapy issues. Give PGE_1. At the time of catheterization, if the RV is of reasonable size, you can

Quick Quiz

- In an infant with tricuspid atresia, when will cyanosis occur?
- How does the ECG in tricuspid atresia differ from tetralogy of Fallot and complete transposition?
- What is the right atrial finding in Ebstein anomaly?
- What drug will improve cyanosis in a child with pulmonary atresia with intact ventricular septum? Why?
- What is total anomalous pulmonary venous return?
- How do infants with total anomalous pulmonary venous return present?
- What is the CXR finding in total anomalous pulmonary venous return?

attempt pulmonary valvuloplasty. If the valvuloplasty works, keep the PGE_1 going (to keep the PDA open) for several more days, so that the RV can have time to remodel and become a useful pump to the lung. After a period of time, a 2-ventricle repair may be done. If the valvuloplasty doesn't work, perform surgery. Those defects with very poorly formed RV are treated similarly to tricuspid atresia—shunting and, later, the Fontan approach. The type depends on the severity of lesion, but this topic is beyond the scope of the general Peds Board exam.

BI-DIRECTIONAL SHUNTS (RIGHT-TO-LEFT AND LEFT-TO-RIGHT)

Total Anomalous Pulmonary Venous Return

Total anomalous pulmonary venous return makes up about 1–2% of all congenital heart lesions seen in the first year of life.

Usually, there is no direct connection between the pulmonary veins and the LA. The pulmonary veins go either to the RA or to other systemic veins that then drain into the RA.

3 main types of anatomic connections occur: supracardiac, cardiac, and infracardiac (infradiaphragmatic). 33% will have pulmonary venous return via a left vertical trunk into the left innominate vein and then into the superior vena cava. 25% will go below the diaphragm, connect with the ductus venosus, and then go into the inferior vena cava. The other 30–40% or so will connect directly to the RA or the coronary sinus.

The subdiaphragmatic form is most likely to have severe obstruction to pulmonary venous return, and the neonate presents with pulmonary edema and more severe cyanosis. The supracardiac form can also have obstructive problems, but it is much less common. Other cardiac abnormalities occur in ~ 33% of those with total anomalous pulmonary venous return.

A majority of infants present early on with tachypnea and FTT. In those without pulmonary venous return obstruction, cyanosis initially may be minimal. Murmurs are rare early. In those neonates and infants with severe obstruction to pulmonary venous return, early-onset dyspnea is prominent, with pulmonary edema developing rapidly.

In those infants with unobstructive pulmonary venous return to the innominate vein, CXR shows a classic "snowman" or "figure-8" silhouette (Image 12-20). The dilated left vertical vein, innominate vein, and the right superior vena cava sitting next to the dilated heart form the silhouette. In those with obstructive pulmonary venous return, the heart on CXR is normal in size, and the lungs show a diffuse hazy pattern resembling "ground glass," as seen with respiratory distress syndrome. Echocardiogram is diagnostic. Cardiac catheterization is rarely required.

Quick, surgical treatment is necessary for the severely obstructed group. You must begin symptomatic therapy early on to reverse acidemia and hypoxemia. The goal of surgical correction is to get the common pulmonary vein connected to the left atrium.

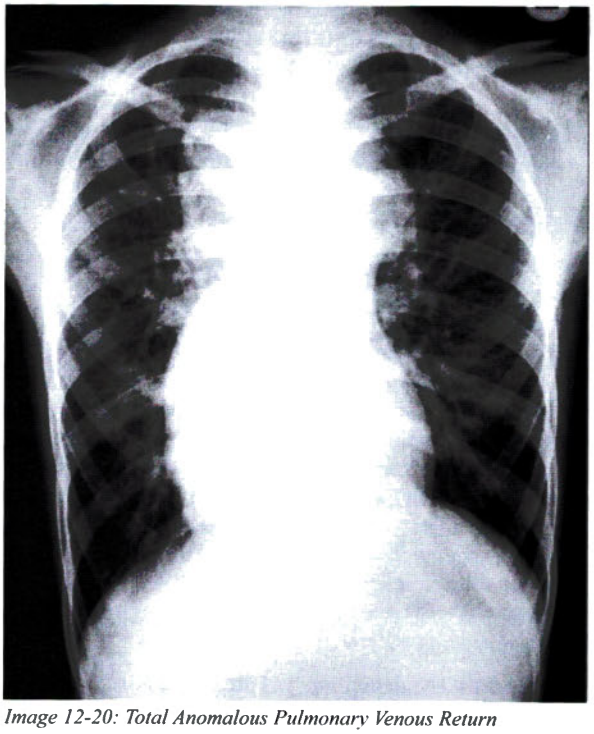

Image 12-20: Total Anomalous Pulmonary Venous Return

Hypoplastic Left Heart Syndrome

This name defines those disorders in which the left side of the heart is underdeveloped. The right side of the heart is dilated and hypertrophied and supports both the systemic and pulmonary circulations using a PDA. Hypoplastic left heart accounts for ~ 25% of all cardiac deaths in the first year of life. Frequently, associated abnormalities occur, including aortic and mitral atresia/stenoses.

Most infants are acutely ill with signs of poor perfusion (lactic acidosis), CHF, and/or cardiogenic shock within the first days or weeks of life. Infants have cyanosis with a grayish color and poor pulses, but they have hyperdynamic cardiac impulses. Pulses may become weaker and then stronger, depending on the patency of the ductus arteriosus.

CXR eventually shows cardiac enlargement and prominent pulmonary vasculature. Pulmonary edema may be present. ECG will show RA and RV hypertrophy. Echocardiogram is diagnostic.

Use PGE_1 to maintain the ductus arteriosus. 2 procedures are possible:

1) Norwood procedure—1st stage: Cut the main pulmonary artery and ligate the PDA. Use the proximal pulmonary artery to reconstruct the ascending aorta and aortic arch to establish output from the RV to the aorta. A systemic-to-pulmonary shunt then reestablishes pulmonary blood flow. The Sano variant places a small RV-to-PA conduit. If the foramen ovale is small, do an atrial septectomy. Perform a bidirectional Glenn procedure (2nd stage, SVC-to-PA shunt) 4–6 months later, followed still later with a modified Fontan procedure (3rd stage, IVC-to-PA connection).

2) Orthotopic heart transplantation has had excellent short-term results to date, but donor hearts are scarce.

Single Ventricle

Single ventricle refers to a variety of disorders in which there is 1 ventricular chamber that receives both the mitral and tricuspid openings (e.g., double inlet left ventricle), or when there is a common AV orifice. The most common of these are morphologically left ventricles without the inflow portion of the right ventricle. Usually, there is a rudimentary anterior and left-sided right ventricular outflow chamber. This connects proximally to the single ventricle through a VSD and distally with a transposed aorta. The pulmonary artery comes off the single ventricle and is posterior in position. Other cardiac anomalies are common and can include dextrocardia, common AV canal, coarctation, and either pulmonic or subaortic stenosis.

Symptoms vary, depending on the degree of PS and the other anomalies. In severe pulmonic stenosis, you will hear a loud systolic murmur and see severe cyanosis. If pulmonic stenosis is mild, there may be increased pulmonary blood flow and minimal cyanosis.

CXR may show a straightened left heart border. The ECG is nonspecific, and the echocardiogram is diagnostic. You may need to perform cardiac catheterization to fully define the abnormalities present.

Treatment is difficult, but prognosis is improving. Palliation is usually possible for infants with decreased pulmonary blood flow by creating either systemic pulmonary or cavopulmonary anastomoses and eventually performing the Fontan procedure. For those with increased pulmonary blood flow, effective intervention has been accomplished by banding the pulmonary artery to control pulmonary blood flow and then by proceeding to a modified Fontan procedure.

Truncus Arteriosus

Truncus arteriosus makes up ~ 1% of all congenital heart lesions. This abnormality occurs when a single arterial trunk comes off from the ventricular chambers. This vessel supplies the coronary, pulmonary, and systemic circulations proximal to the aortic arch. A truncal valve with 3, 4, or more leaflets is present, and this overrides a VSD. The pulmonary arteries come off as a single vessel or as 2 separate vessels from the back of the truncus. A large number of patients with truncus have an associated chromosomal abnormality—partial deletion of chromosome 22 (the "DiGeorge area" of chromosome 22). Uncommonly, they may also have an interrupted aortic arch.

Because the right and left ventricles eject blood at systemic pressure in the common arterial trunk, the coronary, pulmonary, and aortic circulations receive "mixed" venous and oxygenated blood at systemic pressures. Pulmonary blood flow is increased, so significant cyanosis is not common early on.

In the first weeks or months of life, the left-to-right shunt increases, and patients present with signs of left heart failure, dyspnea, wheezing, and FTT. Cyanosis is still not significant because pulmonary flow is often still relatively high. The heart is hyperdynamic, and the peripheral pulses are strong and bounding.

CXR in most will show cardiomegaly with increased pulmonary markings. You will see a right aortic arch in ~ 30–50%. ECG shows RV or combined ventricular hypertrophy. Echocardiogram is diagnostic.

Treatment may initially consist of medical management of CHF, but surgery is necessary. Most infants will die between 3 and 12 months of age without surgery. Closing the VSD leaves the aorta coming off the left ventricle. Remove the pulmonary arteries from the truncus, and

QuickQuiz

- How do most infants present with hypoplastic left heart syndrome?
- What chromosomal anomalies do patients with truncus arteriosus have?
- Differentiate situs inversus from dextrocardia.
- What is the most common aortic arch abnormality? What symptoms does it usually cause?
- What is the most common aortic arch abnormality that causes significant symptoms?
- What congenital disorder is associated with aortic arch abnormalities?

place a valved conduit from the right ventricular wall to the pulmonary arteries to form a new RV outflow tract. Generally, perform surgery at < 3 months of age. The valved conduit will need to be changed at age 3–7 years and again at a later age to allow for growth.

MALPOSITIONS

First, here's what is normal for the anatomy (when thoracic and abdominal structures are correctly placed), known as "situs solitus":

- Right lung with 3 lobes
- Left lung with 2 lobes
- Asymmetric tracheobronchial branching
- Liver with a major lobe on the right
- Left-sided stomach and spleen
- Right-sided venae cavae
- Morphologically distinct atria
- Normal, orderly arrangement of the GI tract

Now, for what's not normal …

Situs Inversus: This is a "mirror-image" configuration of the asymmetric organs and includes the GI tract. Here, all of the asymmetric organs listed above are on the opposite side, so that you have a 3-lobed lung on the left side and the liver on the left. The atria are switched, but the apex may be either right or left.

Right Atrial Isomerism (also termed asplenia or Ivemark syndrome): This is bilateral "right-sidedness" with bilateral, 3-lobed lungs; a horizontal liver with equal-sized lobes; and bilateral morphologic right atria, each with a sinoatrial node. No spleen (asplenia) is usually present. Bowel malrotations are common, as is complex congenital heart disease. These patients are at risk for infections like other asplenic patients.

Left Atrial Isomerism (polysplenia syndrome): This is bilateral "left-sidedness" involving the lungs and the atria. But there are usually 2 to 30, equal-sized spleens (polysplenia) with a combined mass equal to that of a normal sized spleen. This is not the same as "accessory" spleens, which are usually small, isolated spleens in addition to a normal spleen. Again, bowel malrotations are common, as is complex congenital heart disease.

Dextrocardia: If the heart is mainly in the right hemithorax, it is referred to as dextrocardia. The atrial situs can be solitus, inversus, or ambiguous (cardiosplenic). Complete "mirror-image" heart and abdomen (situs inversus totalis) makes up only 10–20% of dextrocardia.

VASCULAR RINGS AND SLINGS

Vascular rings/slings come from the abnormal persistence and/or dissolution of all, or some, of the paired embryonic aortic arches that connect the embryonic truncus arteriosus to the paired dorsal aortas. Some will produce no symptoms. Alternately, they may press on the esophagus or trachea and cause symptoms of dysphagia or breathing difficulties.

The most common aortic arch abnormality is an aberrant right subclavian artery arising from the descending aorta, but it rarely causes symptoms. The artery runs posterior to the esophagus and may indent it from the rear, but it usually does not cause any problems. (It is not even forming a real "ring" or "sling.")

Right aortic arch is very common in tetralogy of Fallot or truncus arteriosus; but, by itself, it rarely causes symptoms.

Double aortic arch (persistence of both right and left 4th arches) is the most common anomaly to cause symptoms. The anomaly results in encircling of the trachea and esophagus, resulting in tracheal compression and respiratory symptoms. The right and left arches indent the right and left sides of the trachea and the esophagus. A CXR usually reveals a right aortic arch, and a barium swallow is diagnostic, revealing the esophageal compression. Look to see if the indentation or compression of the esophagus is anterior or posterior. Vascular rings will cause a posterior indentation, while a pulmonary sling will produce an anterior indentation. Open or thoracoscopic surgery can be curative, with division of the smaller, left posterior arch; this results in opening the constrictive ring.

The right aortic arch (especially if there is an aberrant left subclavian artery) can also be constricting, because of retroesophageal left-sided PDA or ligamentum arteriosum connecting to the left pulmonary artery (loose or incomplete ring). This combo makes indentations on the esophagus and trachea similar to the double arch.

Note: Look for complete or partial DiGeorge syndrome in infants with aortic arch abnormalities!

ANOMALOUS ORIGIN OF LEFT CORONARY ARTERY

With anomalous origin of the left coronary artery, the left coronary comes off the pulmonary artery while the right continues to come off normally from the anterior aortic sinus. In the fetus, myocardial perfusion is normal. Soon after birth, however, the pulmonary artery pressure falls, and blood flows from the right coronary through collateral vessels into the left coronary, then back into the pulmonary artery. This circulation makes a small, left-to-right shunt, and the blood that should be going to the heart is diverted to the lungs. This results in ischemia of the anterolateral wall of the left ventricle.

Infants present 2 weeks–6 months of age with heart failure from MI or ischemia. Poor feeding, tachypnea, and respiratory symptoms are most common, although some will have episodes of restlessness/crying, as though in pain. Cardiomegaly is prominent. ECG will show an anterolateral infarct pattern with abnormal Q waves in I, aVL, and the left anterior chest leads; additionally, ST and T wave changes are common. Echo may be helpful, but usually, cardiac catheterization is required. Treatment requires reconnecting the aberrant coronary artery to the aorta.

Lastly, there is a condition that can occur wherein the left or right coronary artery arises from the opposite cusp. In either condition, the affected artery may pass between the aorta and the pulmonary artery. This results in pain, syncope, or sudden death if the artery becomes dilated and compresses the coronary artery. Look for anomalous left coronary artery from the opposite cusp on the Board exam as a possibility in an athlete who reports chest pain with exercise, or a sports event in which a young person "passes out" and dies. (HCM is most common, but coronary artery anomalies are the second most frequent cause of sudden death among participating athletes.)

PULMONARY HYPERTENSION

Pulmonary hypertension has two causes. The most common cause is increased pulmonary blood flow, as seen in large left-to-right shunts (e.g., VSD). The second cause is secondary or primary increase in pulmonary vascular resistance. Also, this second cause may be seen over time in large left-to-right shunts and is secondary to a decrease in the total, cross-sectional area of the resistance vessels (either because of fewer vessels or a narrowing of normal vessels) and increased, abnormal muscle development in the small arterioles. Pulmonary hypertension from increased resistance may result from a variety of diseases—secondary to congenital heart defects with pulmonary overflow, cor pulmonale, recurrent pulmonary emboli, idiopathic/primary, or other disease states, such as SLE. Increased blood viscosity and polycythemia most often results from chronic hypoxia.

Clinically, pulmonary hypertension may present as a narrowly split or single second heart sound with a loud, pulmonic component. A diastolic decrescendo murmur from pulmonary valvular regurgitation may be present. RV failure may occur. Syncope and chest pain are common only in later stages. If pulmonary hypertension is severe, sudden death may occur. CXR may show a large, proximal pulmonary artery. RA and RV hypertrophy may be apparent on the CXR and ECG.

Direct treatment toward correcting the underlying cause, if present. An example is chronic hypoxia due to persistent severe tonsillar enlargement. Once the obstruction is removed, the hypoxia resolves and the pulmonary hypertension slowly resolves. Vasodilators have a variable effect on pulmonary hypertension. Chronic IV PGI_2 infusions may produce long-term reduction in pulmonary vascular resistance. Sildenafil citrate (Viagra®) and endothelial receptor antagonists (bosentan) are also used.

PERICARDIAL DISEASES

ACUTE PERICARDITIS

Acute pericarditis is an inflammation of the parietal pericardium and superficial myocardium that occurs with rapid onset. It presents with chest pain and sometimes fever. A pericardial friction rub, if present, is virtually pathognomonic. The rub is in phase with the heart sounds and usually has 3 components: atrial systole, ventricular systole, and ventricular relaxation. On an ECG, look for elevation of ST segments in most leads as the initial finding, followed by a return to normal of ST segments with T wave flattening and inversion.

Etiologies of pericarditis vary, but infections are common in children—especially viral infections (coxsackie A and B, echovirus, adenovirus). In certain areas of the U.S., histoplasmosis and coccidioidomycosis can cause pericarditis. Common childhood bacteria, such as staphylococci and pneumococci, also can be responsible. Tuberculosis is generally going to cause more of a chronic scenario. Drugs (phenytoin, hydralazine, and procainamide) have been implicated, as well as chest trauma/surgery.

Treatment includes nonsteroidal, antiinflammatory agents; occasionally, prednisone is required. If there is significant compression of the heart with tamponade, pericardiocentesis may be needed. Use antibiotics if the etiology is bacterial, and perform drainage for purulent effusions. For tuberculosis disease, some also recommend an early pericardiectomy because of the eventual high risk of constrictive pericarditis. Uremic pericarditis is treated by dialysis.

QuickQuiz

- An athlete reports chest pain with exertion that is relieved with rest. He does not have IHHS. What is the next most likely anomaly?
- What does a pericardial friction rub almost always indicate?
- What are the classic ECG findings in acute pericarditis?
- Muffled heart sounds may be indicative of what disorder?
- What is Kussmaul sign?
- In what pericardial diseases are you likely to see Kussmaul sign?
- During cardiac tamponade, what would you expect the end-diastolic pressures to be in the 4 chambers of the heart?

PERICARDIAL EFFUSION

Pericardial effusion (Image 12-21) can vary in character as serous, purulent, or bloody. It pushes the parietal pericardium away from the heart. Pericarditis can be associated with effusion. If the effusion is large, the heart sounds may sound muffled. Pericardial effusions have the same etiologies and treatments as mentioned above with pericarditis.

CARDIAC TAMPONADE

Cardiac tamponade is a life-threatening emergency. It can occur with just a little bit, or a large amount, of fluid present. The pericardium itself becomes "tense," causing the pressure in the pericardial cavity to increase, resulting in impaired filling and relaxation during the cardiac cycle. Ventricular end-diastolic, atrial, and venous pressures all rise on both sides of the heart by equal amounts.

Cardiac output falls with tachycardia, and hypotension occurs with a narrow pulse pressure.

Remember: Normally, with inspiration the pressure in the intrathoracic cavity drops, and abdominal pressure increases so that systemic venous return increases. With tamponade, however, the increase in venous return cannot be accommodated. This causes the jugular venous pressure to rise with inspiration, known as Kussmaul sign (more commonly, it is seen in constrictive pericarditis). Also remember: Normally with inspiration, aortic blood pressure can fall 4–10 mmHg. With tamponade, the aortic pressure will fall > 10–15 mmHg, resulting in "pulsus paradoxus."

On the Board exam, look for jugular venous distension with no collapse during diastole and pulsus paradoxus as your clue that tamponade is occurring. Another thing to look for is a Board question that gives you diastolic pressure readings in the heart, and they are all the same. It is either tamponade or constrictive pericarditis. Kussmaul's is more commonly seen with constrictive pericarditis. Finally, they may present a patient with rising jugular venous pressure (above), dropping systolic blood pressures, and quiet, muffled heart sounds. These three findings are known as Beck's Triad and are associated with tamponade physiology.

Treatment of tamponade is removal of the fluid via pericardiocentesis.

CONSTRICTIVE PERICARDITIS

This is uncommon in children, but if it occurs, it is most likely due to tuberculosis, previous bacterial pericarditis, or mediastinal radiation. Kussmaul sign occurs frequently, and pulsus paradoxus can also be present. End-diastolic pressures in all 4 chambers are equal. CT or MRI shows the thickened pericardium best; CXR also may show calcified pericardium. Treat by removing the restrictive fibrous tissue.

POSTPERICARDIOTOMY SYNDROME

Postpericardiotomy syndrome can follow any surgery in which the pericardium is disturbed or opened. This syndrome results from an immune-mediated inflammation occurring postoperatively. Most of the attacks occur within the first 1–4 weeks post-surgery, but they can occur as far out as 6 months. It presents as acute pericarditis, pericardial effusion, and fever. Pleural effusions also are common. ESR is increased. Patients who develop this have high titers of heart-reactive antibody, and ~ 75% have an acute rise of antibodies to adenoviruses, coxsackie B, or CMV.

Treat with bed rest and aspirin 80–100 mg/kg/day. Once the acute attack is under control, gradually wean off the aspirin over 6 weeks. Recurrences occur in up to 10–15% of patients. Steroids are needed on occasion.

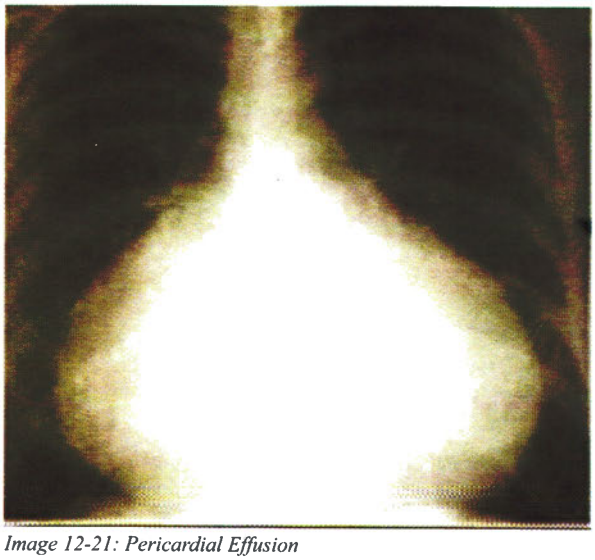

Image 12-21: Pericardial Effusion

CONGESTIVE HEART FAILURE (CHF) TREATMENTS

WHAT IS COVERED HERE

Since CHF is covered under the specific causes scattered throughout the text, we're not going to spend a lot of time discussing the specific etiologies. Realize that just about anything that disrupts myocardial function may cause CHF. We will discuss the drugs in cardiac care because you may be asked about the pharmacologic effects of these agents. We'll break them down by class.

INOTROPIC AGENTS

Mechanism

These improve the contractility of the heart. The goal is to increase cardiac output and improve perfusion to vital organs and tissues.

Dopamine

Dopamine is used extensively to manage acute "low-output" states. It increases myocardial contractility by stimulating norepinephrine release from cardiac adrenergic receptor sites. It also dilates peripheral vascular beds, where it acts on dopamine receptors to inhibit norepinephrine release. This occurs at low doses. At these lower doses, coronary and renal perfusions are enhanced. At higher doses, α-adrenoreceptor stimulation causes vasoconstriction, increased afterload, and a decrease in renal blood flow.

Dobutamine

Dobutamine is a synthetic analog of dopamine. Dobutamine has β_1-adrenergic effects that stimulate myocardial contractility. It is also a mild vasodilator. Dobutamine will usually increase cardiac output without increasing heart rate or blood pressure.

Epinephrine

Epinephrine stimulates both α- and β-adrenoreceptors. It is usually used post-operatively, when dopamine and dobutamine are ineffective. In low-output states, such as the post-op setting, it will dilate vasoconstricted beds and has potent, inotropic effects. At higher doses, it may cause systemic vasoconstriction.

Milrinone

This drug belongs to the class of nonglycoside, noncatecholamine drugs. It has both positive inotropic and vasodilator effects by inhibiting phosphodiesterase Type III. It can be useful in those patients who become desensitized to dopamine and who have had repeated infusions, because these drugs act beyond the receptor site. It can also be used to provide afterload reduction, in addition to inotropic support, in selected patients.

Digoxin (Digitalis Glycosides)

Digoxin works by inhibiting the sodium pump (Na^+-K^+ ATPase) at its receptor site; this causes intracellular sodium increases, which then causes increased intracellular calcium due to activation of the Na^+-Ca^{2+} exchange mechanism. Increases in intracellular calcium cause increased inotropic response. Another effect of digoxin is to inhibit sympathetic responses and increase parasympathetic tone, and it thus decreases metabolic demands on the heart.

Monitoring of digoxin use has gotten away from looking at digoxin levels. Generally, look for clinical response and ECG changes that might indicate digoxin toxicity. Levels are more useful if you are concerned with drug interactions.

Know that digoxin levels are increased with quinidine, verapamil, amiodarone, beta-blockers, tetracycline, and erythromycin. Alternatively, digoxin levels can be decreased by rifampin, neomycin, and cholestyramine.

Acute toxicity usually presents with nausea, vomiting, and diarrhea. Be especially aware of color-vision changes, confusion, or vertigo. Palpitations and arrhythmias (AV block, SVT, or VT) are common also. If toxicity is severe, you may give digoxin antibodies (Fab fragments, Digibind®).

DIURETICS

Overview

Diuretics are the principal agents for control of pulmonary, as well as systemic, venous congestion. They increase sodium loss by increasing renal excretion of sodium and other ions by inhibiting tubular resorption of sodium at various sites in the nephron.

Loop Diuretics

These include furosemide, bumetanide, and ethacrynic acid. These inhibit the Na-K-Cl cotransporter in the ascending limb of the loop of Henle to block sodium and chloride resorption. Doing this causes sodium, potassium, hydrogen, and chloride ions to accumulate in the tubular lumen and then flush out in the urine. Side effects can include hypokalemia, hypochloremia, hyponatremia, and metabolic alkalosis. Loop diuretics also increase calcium excretion. Furosemide has been associated with nephrocalcinosis when used in the premature infant.

Agents that Affect the Cortical Diluting Segment

These diuretics are the thiazides and metolazone. They block sodium and chloride resorption in the cortical diluting segment of the renal tubule and the proximal portion of the distal convoluted tubule. Because

Quick Quiz

- Differentiate the effects of low-dose and high-dose dopamine.
- What does epinephrine do?
- Which electrolytes may be depleted with loop diuretics?
- Which diuretic may actually increase serum potassium levels?
- What is the most common cause of syncope?

of this action, more sodium reaches the distal tubules, where it can be exchanged with potassium. Metolazone is rarely used outside the hospital except for unusual cases, because it can cause a profound diuresis with volume depletion. Thiazides increase potassium loss and decrease calcium excretion.

Potassium-sparing Diuretics

The most commonly used potassium-sparing diuretic is spironolactone. It acts on the distal tubule at the site of aldosterone activity and inhibits sodium-potassium exchange. Spironolactone impairs both the resorption of sodium and the excretion of potassium and hydrogen ions, resulting in less potassium loss. Spironolactone recently has been shown to be effective in reducing mortality in severe CHF in adults. Monitor patients for hyperkalemia, especially if you are supplementing potassium or using an ACE inhibitor (see below). A much less common side effect (but shows up on Boards!) is gynecomastia developing from the neurohormonal interactions.

Atrial Natriuretic Peptide

Nesiritide IV infusions are proven effective for diuresis in adults with CHF, particularly those presenting with dyspnea as a chief complaint. Initial trials are beginning in pediatrics, but there is limited data. The use of serum BNP or pro-BNP (brain natriuretic peptide) levels may be helpful as a screen for CHF. Serum BNP levels are elevated when dyspnea is due to cardiac failure, rather lung disease.

VASODILATORS

These agents are important in remodeling or manipulating ventricular load.

ACE Inhibitors

ACE inhibitors constrain the maladaptive neurohumoral forces initiated by the renin-angiotensin-aldosterone system. ACE inhibitors cause ventricular remodeling and increase ventricular efficiency. They also decrease afterload. They are useful in patients with chronic, severe CHF, as in dilated cardiomyopathies, in left-to-right shunts, and in other causes of CHF. They are not useful in restrictive cardiomyopathies or in those with diastolic dysfunction. Side effects to be on the lookout for: hyperkalemia, elevated creatinine, and angioedema. You may see cough in adults, but this is less common in children.

Sodium Nitroprusside

This agent is used as an acute vasodilator when afterload reduction needs to occur quickly. It probably works by forming nitric oxide, which is a potent vasodilator. Cyanide toxicity is a concern if given for > 48 hours. If a patient is in the ICU with an unexplained metabolic acidosis, consider a cause to be prolonged use of sodium nitroprusside. Treatment options, after discontinuing the drug, would be sodium thiosulfate or hydroxocobalamin (vitamin B_{12}).

BETA-BLOCKERS

Beta-blockers for CHF? This used to be a contraindication. Now we know that low doses of beta-blockers can be very helpful in those with dilated cardiomyopathy and chronic CHF. It appears that they decrease deleterious sympathetic activity, with workload and ventricular relaxation both improving. Selective β_1 blockers, such as metoprolol, have become the most commonly used in adults and are increasingly used in children. Another agent, carvedilol, has both β_1 blockade and vasodilator effects and is being used more commonly as well.

SYNCOPE

Syncope is defined as a transient, complete loss of consciousness and postural tone. It is fairly common in childhood; ~ 20% will experience it at some point.

With syncope, the brain basically has an acute transient loss of cerebral perfusion. Lots of things can do this, and not all are cardiac in nature.

The most common cause in children is vasovagal, vasodepressor, or neurocardiogenic syncope—the "simple fainting attack." It is most commonly seen in adolescents and can be triggered by injury, fear, pain, anger, disgust, or the sight of blood, among other things. The patient feels dizzy or weak but does not have true vertigo. Often, it is accompanied by a prodrome of nausea, blurred vision, and a "rushing of water-like" sound in the ears. BP falls and the patient becomes pale and clammy and has either maintained heart rate/tachycardia or more commonly may have profound bradycardia (cardioinhibitory) and loss of consciousness. Injury is rare because, usually, the patient can tell it is coming. Lying down will alleviate the symptoms. Orthostatic hypotension is also quite common, usually occurring with prolonged standing in a warm

environment or on quickly arising from a supine to standing position. It is more likely in those with volume depletion, impaired autonomic nervous systems, and with certain drugs (vasodilators, antiarrhythmics, antidepressants, cocaine, or alcohol). Postural orthostatic tachycardia syndrome (POTS) is a related disorder in which tachycardia is a common finding.

Cardiac etiologies are less common and include obstructive heart lesions (severe aortic or pulmonic stenosis, IHHS/HOCM, tetralogy of Fallot, abnormal coronary arteries) and arrhythmias (SVT, VT, sinus node dysfunction, AV block, long QT syndrome).

Vasovagal syncope can occur when a susceptible patient swallows cold food/liquid, has sudden decompression of a full bladder, or brushes their hair. These quickly result in severe bradycardia.

The nonvascular etiologies include atypical seizures, migraines, hyperventilation, cough syncope, hysterical syncope, and sudden rises in intracranial pressure. Breath-holding spells do not usually present as simple syncope.

Diagnose by using the history and physical examination to get to the underlying cause. If there are no findings of heart disease or gross autonomic dysfunction, simple vasovagal or vasodepressor syncope is most likely. If you suspect arrhythmia, order a 24-hour Holter and ECG. Echocardiography is of little benefit unless you suspect a cardiac abnormality.

In the past, to confirm vasovagal or vasodepressor syncope, the tilt-table test was often ordered; today, it is rarely needed except in cases where the diagnosis is unclear by simple history and physical examination. Increasing fluid and salt intake treats vasodepressor syncope. Discourage caffeine. Beta-blockers may (or may not) be helpful. Florinef, a mineralocorticoid, and α-agonists, such as midodrine, have been successful.

CHEST PAIN

ACUTE VS. CHRONIC

The patient's complaint of "my chest hurts" is very common in children. Adult chest pain immediately makes one think of cardiac etiologies. With children, this frequently becomes the greatest concern to the parent (and/or child) as well. It is best to think of chest pain in 2 categories—the "acute-onset, severe" and the "chronic and recurrent." Using this as a guide, you can usually sort things out fairly quickly.

ACUTE-ONSET, SEVERE CHEST PAIN

Presentation

These kids come in looking upset and distressed. They have that "I'm going to die" look on their face. They more likely show up in emergency departments or acute care settings. Generally, they are having the chest pain when you see them. Focus on the pain and associated symptoms and determine if there are any predisposing medical conditions. Remember: Chest pain in children is most likely noncardiac!

Pericarditis

Pericarditis is described as severe, substernal chest pain that is squeezing or tightening in character. This aspect resembles angina. The pain, however, is worse with movement, and even breathing will exacerbate it. Usually, the patient will prefer to lean forward and will not want to lie down. Typically (especially on the Board exam), there is a pericardial friction rub. Pericarditis is the most common cause of cardiac chest pain in children. See the pericarditis discussion above for more.

Angina / MI

This is the most feared, right? But it is very, very rare in children. Pain is severe, pressure-like, and substernal. It can radiate to the neck or arms. Usually, it is exertional in character and relieved with rest. Look for signs of ischemia on the ECG: ST-segment elevation and T wave changes in the area of affected myocardium and reciprocal ST-segment depression in the corresponding "opposite" leads. Look for cocaine/crack use in the adolescent or a history of Kawasaki disease. If coronary ischemia is suspected, use of troponin and CK isoenzymes may be helpful.

Arrhythmia

SVT is the most likely cause of acute chest pain if an arrhythmia is the etiology. Myocardial ischemia can occur with very fast rates and be similar to angina in character. Syncope or lightheadedness is common. The pain should go away as quickly as the arrhythmia resolves. Perform an ECG when the chest pain is occurring or document very fast heart rates for diagnosis.

Aortic Dissection

The pain in aortic dissection is described as sharp and "tearing." Look for history or findings of Marfan or Ehlers-Danlos syndromes. Also look for it in any child with severe chest pain after trauma or hemopericardium. Quick surgical intervention is mandatory. Diagnose with an MRI, CT, or transesophageal echo.

Noncardiac Causes

Spontaneous pneumothorax causes severe, unilateral chest pain that is accompanied by dyspnea. Findings on physical exam are usually diagnostic, with unilateral or absent breath sounds on the affected side. A history of asthma, CF, Marfan syndrome, or trauma increases the likelihood. In adolescents with HIV risk factors, also think of *Pneumocystis* as an etiology. Viruses can also be responsible and produce mini-epidemics in community settings.

Quick Quiz

- If you suspect an arrhythmia as an etiology for syncope, what testing should you perform?
- What do you do if you suspect vasodepressor syncope?
- What illicit drug is associated with acute MI in young people?
- An adolescent with Marfan syndrome presents with acute chest pain that is "tearing" and radiating to his back. What should you immediately be concerned about?
- What type of chest pain occurs over the rib/cartilage junction and is always reproducible with palpation over the area?

Gastroesophageal reflux (GE reflux) can produce symptoms that mimic angina. Usually, there is a strong relationship to meals and aggravation with lying supine. Esophageal spasm or foreign body can also cause chest pain.

Irritation of the diaphragm can radiate to the shoulder and lower chest. Lower lobe pneumonia can cause this. Hepatic and splenic abscesses can present with chest pain. Pancreatitis can also present this way, though more rarely.

CHRONIC AND RECURRENT CHEST PAIN

Typically, these children do not have the pain when you see them in the office setting. Examination is usually normal.

Musculoskeletal Chest Wall Pain

This is the most common cause of identifiable chest pain in children. The pain is usually very localized and does not radiate. It is sometimes reproducible with chest wall palpation. The pain frequently becomes exacerbated with exercise, raising the anxiety level about cardiac pain. Athletes frequently have localized pain from working out/exercising. Treatment is reassurance for most and mild analgesics (acetaminophen or nonsteroidal antiinflammatory drug).

Costochondritis is pain and tenderness of the anterior chest at the costochondral or costosternal articulations. No swelling is noted. The pain can be mild or severe and is almost always unilateral. Most commonly, it occurs at the left 4^{th}–6^{th} costochondral junctions. It can follow a viral illness or exercise. It is always reproducible with palpation over the area and usually resolves in a week or less. Treatment with NSAIDs can be helpful.

Tietze syndrome is pain and swelling of the anterior chest wall, normally involving the 2^{nd} or 3^{rd} costochondral junction on one side. Pain and swelling come and go and can last months to years. Look for varicella zoster in particular!

Precordial catch is the sudden onset of severe, sharp, or shooting chest pain that is localized at the cardiac apex area. Many cardiologists feel it is one of the most common etiologies for chest pain. It lasts 30 seconds to a few minutes and then resolves. It typically occurs at rest and can recur several times a day. It is worse with deep inspiration. Its etiology is unknown.

Slipping rib syndrome occurs in the 8^{th}, 9^{th}, or 10^{th} ribs at the anterior tip of each. These ribs do not attach to the sternum directly, but are attached by fibrous tissue. A lower rib can move up and override the upper rib, resulting in severe pain that may last for hours or days.

Lung Etiologies

Exercise-induced asthma is a common cause of chest pain in children. Children complain of deep, substernal chest pain and "tightness" that worsens 5–10 minutes into recovery, then lessens over the next 30 minutes or so. Children with chronic asthma are also at risk.

The "stitch" has become more common. Pain is felt in the right upper quadrant of the abdomen and right costal margin, with occasional radiation to the right shoulder. The pain is sharp with a cramp-like sensation. It occurs while running or walking and is relieved by rest.

GI Causes of Chronic Chest Pain

GE reflux with esophagitis is seen more commonly today. The pain is retrosternal in nature and worsens with meals and lying down. Manometry and esophagoscopy are diagnostic. Most will attempt a trial of antacids, histamine blockers, or proton pump inhibitors before proceeding with diagnostic testing because symptoms are fairly classic. Esophageal spasm, achalasia, and foreign body are less common in children.

Heart

Cardiac causes of chronic, recurring chest pain are uncommon. Ischemic pain is rare, but may result from known cardiomyopathy, obstruction (AS), or coronary disease. The most common coronary artery anomaly in children is anomalous origin of the left coronary artery; as discussed previously, this usually presents in infancy. Kawasaki disease is the most common acquired coronary disease, with resultant coronary aneurysms and/or stenosis.

Whether mitral valve prolapse (MVP) results in chest pain in children is controversial. Controlled studies do not indicate a correlation between MVP and chest pain in pediatric patients.

Psychogenic Etiologies

Depending on the cardiologist you talk to, psychogenic factors are probably responsible for at least some chronic chest pain in children and adolescents. Usually, a history of a particular, specific situation or stressful event can be associated with the onset of pain in these settings; e.g., death of parent, divorce, school failure, family member diagnosed with coronary artery disease, or abuse. Pain is usually vague and difficult to localize or describe. Tenderness may be found on palpation in unusual locations.

CARDIOVASCULAR PREPARTICIPATION SPORTS SCREENING

Sudden death in the young athlete is a rare but devastating event. Most recent estimates are that the incidence of sudden death in young athletes is approximately 100 cases per year. Know that the most common cause of sudden death in the young athlete in the United States is hypertrophic cardiomyopathy (this is the "800-pound gorilla", the #1 cause!!). Other important causes include: coronary artery anomalies, *commotio cordis* (a blow to the chest resulting in v-fib), aortic rupture (Marfan syndrome), and "other" (long QT, WPW, aortic stenosis). Strategies to reduce sudden death in high school and college athletes are geared toward identifying high-risk athletes, treating underlying conditions that might predispose to sudden death, and/or excluding the athlete from participation in athletics, when appropriate.

There has been much debate on how best to identify at-risk athletes. Know that in the United States, routine ECG or ECHO screening of all high school and college athletes is not recommended. Rather, the American Academy of Pediatrics and others recommend a screening approach to identify high-risk athletes. This includes a targeted history and cardiovascular-focused examination. All athletes should be screened before participation in high school or college sports. Look for exertional syncope, near syncope, chest pain, excessive fatigue, or shortness of breath in the history. Also obtain a family history looking for premature death or disability from heart disease in young relatives (< 50 years of age), and, of course, a family history of Marfan's, hypertrophic cardiomyopathy, long QT. On physical examination, look for stigmata of Marfan's, elevated blood pressure and absent or diminished femoral pulses, and pathologic murmurs. If any of the above are positive, refer to a pediatric cardiologist for further evaluation!

PREVENTIVE CARDIOLOGY

It is well established that adult cardiovascular disease (coronary artery disease, hypertension, stroke) has its origins many decades before the disease is manifest in adulthood. Thus, landmark studies, such as the Bogalusa Heart Study, the Muscatine Study, and others, have documented that risk factors for adult heart disease can be identified in childhood (such as hyperlipidemia and hypertension), that these risk factors "track" into adulthood, and that they are associated with an elevated risk for adult cardiovascular disease. Furthermore, autopsy studies have documented fatty streaks and even raised fatty lesions in the aorta of children, adolescents, and young adults. The extent of these fatty streaks and raised lesions correlate with risk factors, such as serum cholesterol and LDL (low density lipoproteins—the "bad" cholesterol).

There is no question that promoting healthy lifestyles in all children is a very important strategy to reduce the burden of cardiovascular disease later in life. These strategies include proper diet (reduced saturated fats), regular exercise, and tobacco avoidance. In addition, identification of "at-risk" children and screening them for hyperlipidemia is recommended to supplement the overall healthy lifestyles strategy.

Know that in the United States, we use a targeted screening method to identify hyperlipidemia in childhood—i.e., not all children need blood testing. Specifically, it is recommended that a fasting lipid profile be obtained in children in whom there is a family history of:

- Myocardial infarction
- Stroke
- Peripheral vascular disease
- Sudden cardiac death in a parent or grandparent < 55 years of age (or even the identification of coronary artery disease by diagnostic testing, such as a cardiac catheterization)
- A parent with a total cholesterol of > 240 mg/dL

or

- If the family history is not known
- If there are other risk factors present, such as obesity or smoking

The latest recommendations are that lipid screening of such children should occur as early as 2 years of age (but certainly before 10 years of age!). If the lipid profile is normal, repeat in 3–5 years. For children found to have elevated triglycerides or low HDL (the "good" cholesterol), weight management should be the treatment of choice (nutritional intervention and increased physical activity). For children with elevated LDL levels, intensive nutritional counseling should be provided. For those children > 8 years of age with LDL > 190 mg/dL (or > 160 mg/dL if there is a family history of early cardiovascular disease or 2 additional risk factors, or > 130 mg/dL if diabetic), drug therapy should be considered if lifestyle interventions alone fail to lower lipid levels.

While there are a number of cholesterol-lowering drugs to consider, statins are becoming increasingly recognized as the drugs of choice, particularly in children > 10 years of age! Needless to say, these children require expert monitoring.

QuickQuiz

- Know Table 12-3.
- What are the only instances in which post-procedure antibiotics are recommended?
- Which heart valves are most commonly affected in rheumatic fever?
- List the major and minor Jones criteria for rheumatic fever.
- Describe the arthritis of rheumatic fever.

ANTIBIOTIC PROPHYLAXIS FOR SBE

Antibiotic prophylaxis recommendations have changed quite a bit! In 2007, new guidelines came out, and now very few conditions require prophylaxis!

SBE prophylaxis for dental procedures, respiratory procedures, or infected skin procedures only in the presence of:

- Prosthetic cardiac valve
- Previous history of endocarditis
- Congenital heart disease in certain instances
  - Unrepaired cyanotic heart disease
  - Completely repaired with prosthetic material or device for 6 months post-procedure
- Cardiac transplant recipients who develop cardiac valvulopathy

Other key points:

- Antibiotic prophylaxis is no longer recommended for any other form of CHD (other than those listed above).
- No antibiotic prophylaxis for GU or GI procedures!

[Know] Table 12-3. If the patient is already on chronic amoxicillin/penicillin, the prophylaxis antibiotic should be of a different class.

RHEUMATIC FEVER

CAUSES / SIGNS & SYMPTOMS

Rheumatic fever (RF) is a disease that follows infection with pharyngeal strains of group A streptococci (*Streptococcus pyogenes*). It occurs most commonly in children ages 5–15 years. Those with a previous history of rheumatic fever have the highest risk of recurrence.

Aschoff bodies are pathognomonic for rheumatic fever. Palisading giant cells and swelling and fragmentation of collagen is seen. The mitral and aortic valves are affected most commonly. Joints develop reversible swelling with fluid accumulation of synovial membranes and in the joint space proper. Subcutaneous nodules are similar to Aschoff bodies and are granulomas with localized collagen infiltration.

The clinical manifestations—known as the Jones criteria—are frequent Board exam questions, so know them!

There are 5 major manifestations:

- Carditis
- Chorea
- Subcutaneous nodules
- Polyarthritis
- Erythema marginatum

There are also minor manifestations:

- Arthralgia
- Increased ESR
- Prolonged PR interval
- Fever
- Increased C-reactive protein

To make the diagnosis, you must have 2 major, or 1 major and 2 minor, manifestations and evidence of a recent or concurrent *Streptococcus pyogenes* infection.

MANIFESTATIONS

Arthritis

The RF arthritis is traditionally an acute, migratory polyarthritis with fever. The joints are red, hot, swollen, and

Table 12-3: Prophylactic Regimens—Dental, Oral, and Respiratory Procedures

Situation	Antibiotic	Regimen (no post-procedure doses!)
Standard general prophylaxis	Amoxicillin	50 mg/kg orally 1 hour before procedure (max 2 g)
Unable to take oral medications	Ampicillin	50 mg/kg IM/IV within 30 mins before procedure (max 2 g)
Allergic to penicillin	Clindamycin or Cephalexin or cefadroxil* or Azithromycin or clarithromycin	20 mg/kg orally 1 hour before procedure (max 600 mg) 50 mg/kg orally 1 hour before procedure (max 2 g) 15 mg/kg orally 1 hour before procedure (max 500 mg)
Both allergic to penicillin and unable to take oral meds	Clindamycin or Cefazolin**	20 mg/kg IV within 30 mins before procedure (max 600 mg) 25 mg/kg IM/IV within 30 mins before procedure (max 1 g)

*Note: Cephalosporins should not be used if the PCN allergy is an immediate-type hypersensitivity reaction.
**Note: The oral doses are given 1 hour before the procedure, whereas the IM/IV doses are given within 30 min.

very tender. It is painful to move them. Larger joints are more commonly affected. Usually, as pain and swelling subside in one joint, another will become painful and swell. The arthritis usually lasts < 1 month and is very effectively treated with aspirin.

Carditis

Some patients with carditis are asymptomatic. The disease can affect the valves (endocardium), myocardium, or pericardium. Murmurs are the most common findings on examination. Most common is an apical pansystolic murmur of mitral regurgitation. Some patients with moderate-to-severe rheumatic mitral regurgitation have a soft, mid-diastolic murmur heard only at the apex. This is known as the Carey Coombs murmur. Aortic regurgitation is the 2nd most common murmur heard. If there is a mid-diastolic apical murmur with aortic insufficiency, it is called an Austin Flint murmur, which is due to impingement of the mitral valve opening by the jet of aortic insufficiency.

Myocarditis can manifest as tachycardia with cardiomegaly or arrhythmias. Prolongation of the PR interval occurs in 20% of cases, but it is too nonspecific to make the diagnosis of carditis itself.

Pericarditis can occur and has the classic symptoms of pericardial pain, friction rub, or marked increase in heart size; but most patients with rheumatic pericarditis are asymptomatic. Pericarditis rarely occurs without pancarditis (valvular and myocardial involvement, in addition to pericardial involvement).

Chorea

Chorea was formerly known as Sydenham chorea and is characterized by sudden, aimless, irregular movements of the extremities associated with emotional instability and weakness. Some liken it to a "break dancer" gone crazy. Since the symptoms usually do not occur with sleep, some children are viewed as "faking it." Chorea usually occurs by itself without any other major symptoms (though 18% do have associated heart disease!), and it may develop months after the inciting infection.

Subcutaneous Nodules

These are small (0.5 to 1 cm), painless swellings occurring over body prominences—usually over the extensor tendons of the hands, feet, elbows, scalp, scapulae, and vertebrae. They occur in crops and can last for months. These are rarely seen.

Erythema Marginatum

This is the least common major condition and occurs in only ~ 5–10% of patients. The rash is an evanescent, pink-to-red macule, often with a clear area in the center and a snake-like serpiginous course. The rash is short-lived, migratory, and does not itch. It blanches with pressure and is usually located on the trunk or proximal arms and legs. This rash is quite rare now.

PROOF OF GROUP A STREPTOCOCCUS

The ability to prove causality is important. Sometimes, though, rapid throat tests or cultures are either not done before antibiotics are given or are negative. Also, many children are carriers for group A streptococcus and not necessarily infected with the organism. As such, the most specific and reliable proof of previous streptococcal infection is found in serum antibody levels. Consistently rising values are more significant than an isolated elevated value. The most widely used test is the antibody formation against streptolysin O (AS or ASO titer). In children, a titer > 333 U is considered elevated. Other tests available include antideoxyribonuclease B (anti-DNase B), antihyaluronidase, antistreptokinase, and anti-nicotinamide adenine dinucleotidase (anti-NADase). A 2-fold rise in titer to one or more of these is usually confirmatory.

The bottom line is that you must have 1 of these:

1) Positive throat culture for group A beta-hemolytic streptococci or positive rapid streptococcal antigen test
   or
2) Elevated or rising streptococcal antibody titer

TREATMENT

In acute rheumatic fever, always give penicillin, even if cultures are negative for group A streptococcus. Either 1.2 million U of benzathine PCN G IM or 600,000 U of procaine PCN q day IM x 10 days is effective therapy. Give erythromycin 1 g orally x 10 days to the PCN-allergic child. Begin prophylaxis immediately after acute therapy to prevent future recurrences of rheumatic fever (see below in Prognosis).

Use salicylates and steroids to control acute symptoms. Aspirin is generally given in a dose of 80–100 mg/kg/day for a minimum of 6 weeks, with gradual tapering over 2–4 weeks. If CHF develops, give patients prednisone 2 mg/kg/day. Chorea does not respond to these therapies, though other agents, such as haloperidol or benzodiazepines, can be helpful.

PROGNOSIS

Around 75% of children with acute rheumatic fever are well after 6 weeks. Beyond 6 months, < 5% are still symptomatic, usually with chorea or carditis. Most children with carditis recover without sequelae, except for those with CHF and pericarditis, a majority of whom develop permanent cardiac damage. The most likely chronic, residual lesions in childhood are mitral insufficiency and aortic insufficiency, and, after childhood, the most likely chronic, residual lesion is mitral stenosis. Those with recurrent disease tend to have the same manifestations during recurrences.

QuickQuiz

- What 2 murmurs are most common in acute rheumatic fever?
- Describe chorea seen in rheumatic fever.
- A child with rheumatic fever presents and is found to be culture-negative for *S. pyogenes*. Should he receive penicillin therapy?
- What cardiac residual lesions are most likely to occur after rheumatic fever in childhood? Which persists more often in adulthood?
- What drugs are used for monthly prophylaxis after acute rheumatic fever? What if the child is penicillin-allergic?

Most recommend continuing prophylaxis for a minimum of 5 years, or until the age of 21, whichever is longer. Those with heart disease usually receive longer-duration prophylaxis well into adulthood, especially if they work around children. Give 1.2 million U of benzathine PCN every 4 weeks or 250 mg of PCN V-K orally twice daily. You can give sulfadiazine or sulfisoxazole 0.5 grams orally on a daily basis for those weighing < 27 kg; increase to 1.0 gram orally and daily for those > 27 kg (but remember: this is for prophylaxis only, not treatment). You may give erythromycin 250 mg twice a day for those allergic to PCN and sulfa drugs.

KAWASAKI DISEASE

Kawasaki disease is an acute inflammatory vasculitis of unknown etiology. It probably represents an autoimmune inflammatory response to an as yet undefined infection. 85% occurs between 6 months and 5 years of age, and it is most common in the Asian population.

The diagnosis is made clinically with fever for 5 days or more and 4 of the following 5 criteria:

1) Conjunctival injection without drainage
2) Cervical lymphadenopathy (unilateral > 1.5 cm)
3) Extremity changes with erythema and edema of the hands and feet and later desquamation
4) Mucous membrane changes with erythema, cracked and peeling lips, and strawberry tongue
5) Polymorphous exanthem—usually macular or maculopapular erythematous, but any rash except vesicles and bullae

Atypical Kawasaki's can be seen with < 4 criteria but with typical coronary findings.

Adjunctive laboratory findings include leukocytosis, elevated ESR and CRP, thrombocytosis often with very high platelet counts, elevated liver enzymes, sterile pyuria, aseptic meningitis, hydrops of the gall bladder (the Boards like this one), and lipid abnormalities.

The patients develop carditis and may have myocarditis, pericarditis, or valvulitis, but the pathognomonic finding is coronary artery aneurysms that develop in 20–25% of cases. These may be bilateral and have a predilection for the proximal vessels. They may be saccular, ectasia, or transient dilation. If greater than 8 mm in diameter, they are "giant" aneurysms and a much greater risk for complications. Aneurysms can occur in other arteries about 1% of the time. About 50% of the aneurysms will "resolve" in time to normal appearing coronaries. Long term they (particularly giant aneurysms) may develop thrombosis, stenosis, and ischemia. This may lead to myocardial ischemia and infarction or death in less than 1% of cases.

Treatment is primarily with IVIG infusion of 2 gm/kg over 12 hours. This improves the fever, inflammatory response, and clinical picture, but it mainly decreases the risk of coronary aneurysms to 5–8%. About 7–8% of children will get a second dose of IVIG for persisting fever and inflammation. If still not responding, IV steroids may be given. Aspirin at antiinflammatory doses (80–100 mg/kg/day) is initially used and later decreased to antiplatelet doses (2–5 mg/kg/day) when the fever resolves. If there are no aneurysms by 6–8 weeks, then the aspirin can be discontinued.

The primary diagnostic modality for evaluating the coronary arteries is echocardiography. This is done initially with the diagnosis, or suspected diagnosis, and then followed at 2–8 weeks to look for aneurysms that mostly develop in the subacute phase. Catheterization is reserved for patients with complex or giant aneurysms or evidence of coronary insufficiency.

The long-term care and follow-up depend on the degree of coronary artery involvement. Those patients with persisting aneurysms are maintained on ASA (or warfarin with giant aneurysms) and followed regularly by cardiology with echocardiography and later stress testing when old enough.

HEART CATHETERIZATION

A good Board question would be to present oxygen saturations from cardiac catheterizations and ask you to interpret them. So let's review these quickly, as well as possible questions.

Normally, there are no intracardiac shunts; therefore, saturations in the right and left heart remain constant as venous (pulmonary and systemic) return flows through the heart and out the great arteries. Normal mixed venous saturation is 75% (70–80%) in the superior vena cava, and this remains constant through the right atrium → right ventricle → pulmonary arteries. Venous blood is then oxygenated and returns to the pulmonary veins with a normal saturation of 95–100%. Again, in the absence of shunting, this should remain fairly constant to the left atrium → left ventricle → aorta (Figure 12-3).

In the presence of a left-to-right shunt, there will be a "step up" in the right heart saturation at the level of the

shunt and then beyond (Figure 12-4). For example, in the presence of a VSD the left ventricular saturation would be normal (95–100%) while the right ventricular saturation would now be increased to 90% because of the flow of oxygenated blood to the right ventricle via the shunt. Structures beyond this "step up" would also retain elevated saturations; therefore, in our example of a VSD, you would also expect the pulmonary artery saturation to be high. So remember: In a left-to-right shunt, the left heart saturations will be normal, and the right heart saturations will be increased initially at the site of the shunt.

The opposite is true for right-to-left shunts. Here, the right heart saturations will remain in the normal range, and the left heart saturations will be decreased at the site of the shunt. For example, if you have a VSD and a right-to-left shunt, you would expect the normal right ventricular saturation, 75%; but now, with decreased left ventricle saturation, it is 85%. Don't forget that the distal structures, such as the aorta in our example, will also be desaturated.

To help you, here are a few figures showing examples in the format they could present you on the Board exam, including PDA (Figure 12-5), ASD (Figure 12-6), and partial anomalous venous return (Figure 12-7).

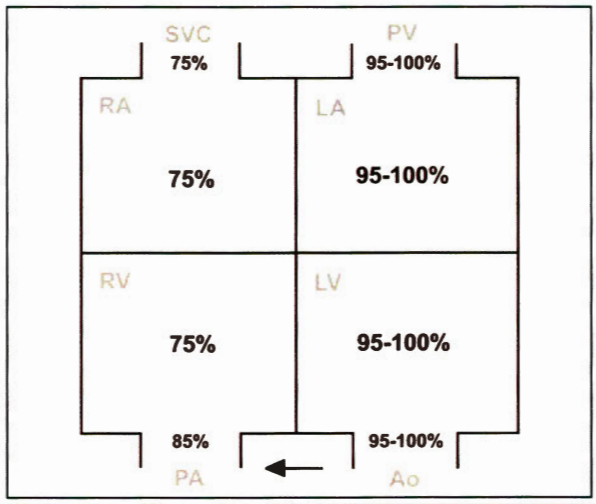

Figure 12-5: PDA

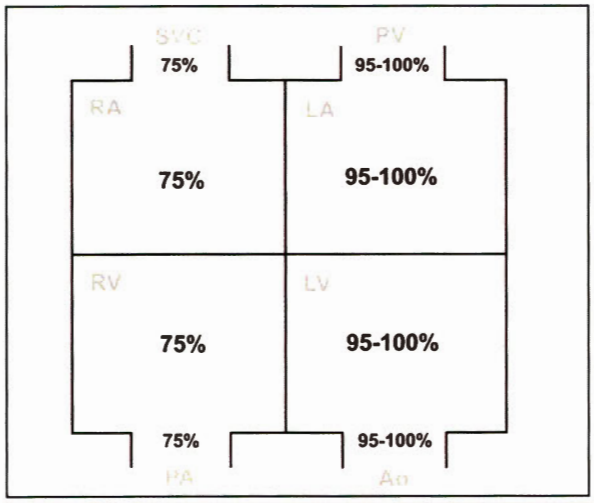

Figure 12-3: Normal Saturations

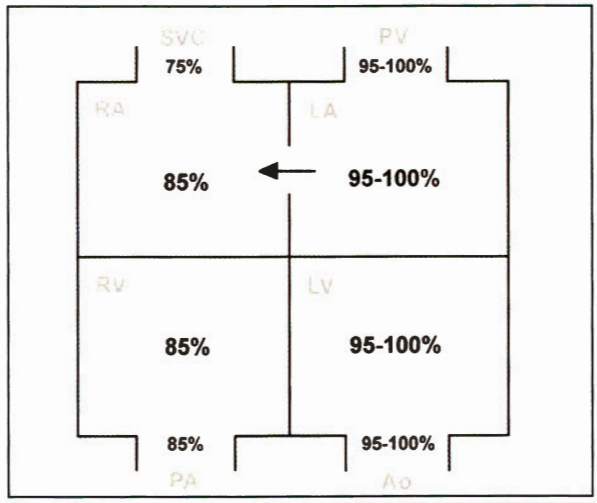

Figure 12-6: ASD

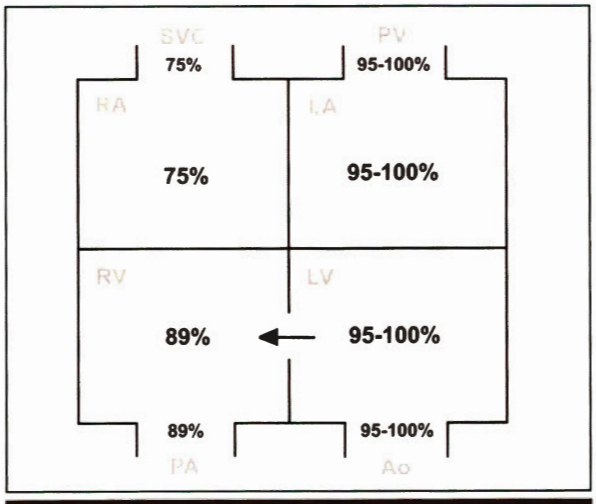

Figure 12-4: Left-to-Right Shunt

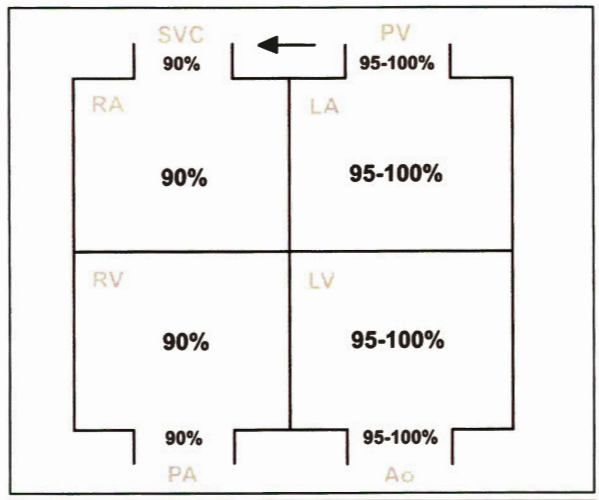

Figure 12-7: Partial Anomalous Venous Return

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PEDIATRICS BOARD REVIEW

PEDS

CORE CURRICULUM

5th EDITION

Authored by J. Thomas Cross, Jr., MD, MPH, FAAP
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RESPIRATORY DISORDERS

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Respiratory Disorders

CONGENITAL DISORDERS OF THE UPPER RESPIRATORY TRACT 13-1
CONGENITAL DISORDERS OF THE NOSE 13-1
Choanal Atresia 13-1
Other Less Common Disorders 13-1
CONGENITAL DISORDERS OF THE TONGUE AND PHARYNX 13-1
Cleft Lip and Palate 13-1
Lingual Ankyloglossia (Tongue-tie) 13-1
Lingual Thyroid 13-1
Thyroglossal Duct Cysts 13-1
Cleft Tongue 13-2
CONGENITAL DISORDERS OF THE LARYNX 13-2
Laryngomalacia 13-2
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CONGENITAL DISORDERS OF THE UPPER RESPIRATORY TRACT

CONGENITAL DISORDERS OF THE NOSE

Choanal Atresia

Choanal atresia is the most common congenital anomaly of the nose and occurs in ~ 1/7,000 newborns. It presents as a unilateral or bilateral, bony (90%) or membranous (10%) septum between the nose and the pharynx. Nearly half of these infants have other associated congenital anomalies. Look for CHARGE syndrome (Coloboma, Heart disease, Atresia choanae, Retarded growth and development, Genital anomalies, and Ear anomalies/deafness).

Symptoms are variable depending upon the infant's ability to breathe through the mouth and the severity of the atresia. Infants with bilateral atresia frequently suck in their lips when they inspire, and they have cyanosis. Those infants who are able to breathe through their mouths have difficulty with breathing when fed.

Diagnosis is confirmed by the inability to pass a firm catheter through each nostril to a depth of about 3–4 cm. CT scan will show the abnormality the best.

Treatment initially involves providing an adequate oral airway. Usually, an orogastric tube is sufficient. You may consider performing neonatal surgery if the infant does not have other contributing factors. You might have to perform a tracheotomy in severe bilateral disease until reconstructive surgery can be safely performed. Unilateral correction can usually be delayed for several years. Restenosis after surgery is common.

Other Less Common Disorders

Congenital perforation and deviation of the nasal septum are rare. If they occur, most are due to birth trauma.

Pyriform aperture stenosis is an abnormality of the anterior nasal aperture that is rare and has symptoms that mimic choanal atresia. Congenital midline nasal masses can include dermoids, gliomas, and encephaloceles. Nasal dermoids may have a dimple or pit on the nasal dorsum and may contain hair. Expect to see recurrent infections.

CONGENITAL DISORDERS OF THE TONGUE AND PHARYNX

Cleft Lip and Palate

A cleft lip occurs because of the incomplete fusion of embryonic structures that surround the primitive oral cavity (Image 13-1). They can be unilateral or bilateral. Cleft palates can involve only the soft palate or may include the hard palate as well (Image 13-2). Cleft palates can vary greatly and may connect to a cleft lip.

Submucosal cleft palates may not be obvious until several years of age. The uvula will commonly be bifid. Occasionally, you will see a blue line in the midline of the soft palate due to a lack of musculature in the midline; this is known as a zona pellucida. A notch of the posterior hard palate may also be palpated.

Treatment requires a multifaceted approach and includes craniofacial teams, speech pathologists, and occupational therapists. You must first address feeding issues. Lip repair usually occurs around 10 weeks of age and palate repair between 9 and 12 months.

Lingual Ankyloglossia (Tongue-tie)

Lingual ankyloglossia is a common disorder in which the lingual frenulum limits the movement of the anterior tongue tip. Infants may have difficulty extending the tongue past the alveolar ridge, which makes breastfeeding difficult. Most newborns can adjust and do well, but some require a frenulectomy, which can be done in the outpatient office setting.

Speech difficulties are rare, especially with the English language. However, one very important social activity—licking an ice cream cone—may be impossible for a child to do, and some children will proceed to frenulectomy.

Lingual Thyroid

A lingual thyroid is more common in girls and occurs when thyroid tissue fails to descend into the neck from its site of origin in the tongue base. Usually, the lingual thyroid will appear as a raised violaceous mass that you will see in the base of the tongue. The thyroid tissue present in the tongue usually does not function properly. Airway obstruction will lead many patients to seek medical attention. You may try thyroid hormone to reduce the size of the thyroid remnant.

Thyroglossal Duct Cysts

Thyroglossal duct cysts are cystic masses in the midline of the neck. Generally, these cysts are asymptomatic unless they become infected. If infection occurs, the cyst may rapidly increase in size and cause respiratory compromise. You must surgically remove thyroglossal duct cysts.

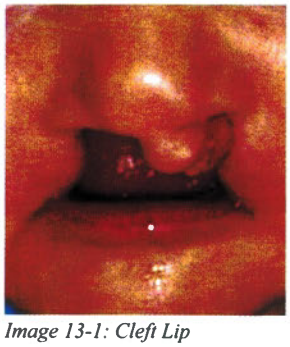


Image 13-1: Cleft Lip

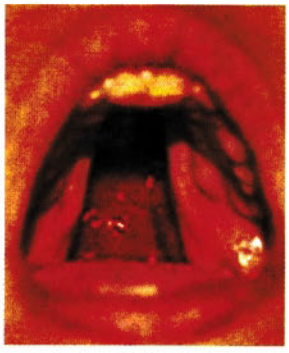


Image 13-2: Cleft Palate

Cleft Tongue

Cleft tongue is part of Oral-Facial-Digital syndrome, Type I, which is inherited as an X-linked disorder. It presents with the cleft tongue, hypoplasia of the nasal alar cartilages, medial cleft of the upper lip, asymmetric cleft of the palate, digital malformations, and mild mental retardation. About half will have hamartomas between the lobes of the divided tongue. Mohr syndrome is an autosomal recessive disorder with lobulated nodular tongue, conductive hearing loss, cleft lip, high-arched palate, hypoplasia of the mandible, polydactyly, and syndactyly.

CONGENITAL DISORDERS OF THE LARYNX

Laryngomalacia

Laryngomalacia is the most common cause of stridor in the newborn. The laryngeal skeleton in some children is just not stiff enough, and inspiration causes significant luminal narrowing, resulting in stridor. The stridor can occur at birth but most commonly is seen at 2 weeks of age. The stridor is more pronounced with agitation. For most, close observation is sufficient, and the cartilage becomes more rigid with age. Most children will outgrow the disorder by 12–18 months of age. In severe cases, feeding may be affected, and nighttime obstructive hypoxia may occur; you may be able to alleviate this by trimming the supraglottis.

Subglottic Stenosis

Subglottic stenosis can cause stridor in the newborn or in the first few months of life. Diagnosis is made by endoscopy. Treat only stenosis that produces symptoms, and treat those cases as early as possible. Some cases require tracheostomy before surgery can be performed. Cases that occur later in life are acquired, and the child usually has multiple other medical problems.

Glottic Webs

Webs can be partial or complete and occur with abnormal development of structures in and around the laryngeal inlet in the developing embryo. Webs can present with abnormal voice or with stridor and respiratory distress. Tracheostomy may be required for severe glottic webs. Webs are associated with the velocardiofacial syndrome. Order genetic testing for 22q11 gene deletions in these children.

Laryngeal Cysts

Cysts of the larynx develop from the mucus-secreting epithelium of the supraglottic region and on occasion from the subglottic region. They present with stridor and hoarseness. Most subglottic cysts are not congenital but are due to secondary causes such as prolonged or traumatic intubation. Remove the cysts with an endoscopic CO_2 laser.

Laryngoceles

Laryngoceles are epithelium-lined diverticula that come from the laryngeal ventricle. They can present with laryngeal obstruction or as a neck mass. Excision is the treatment of choice.

CONGENITAL DISORDERS OF THE LOWER RESPIRATORY TRACT

TRACHEAL DISORDERS

Tracheal Agenesis

Tracheal agenesis is very rare and may present as one of 3 different types:

- Type 1: The proximal trachea is closed off, and the distal part communicates with the esophagus.
- Type 2: The bronchi meet in the midline and communicate with the esophagus through a fistula.
- Type 3: Both bronchi communicate with the trachea separately.

In all 3 types, infants present at delivery in respiratory distress and die shortly thereafter. Suspect this condition if the trachea cannot be intubated even though the larynx is visualized.

Tracheal Stenosis

Tracheal stenosis presents most commonly as a segmental stenosis and can occur anywhere along the trachea. Infants present with severe retractions and dyspnea and have expiratory stridor. Also consider tracheal stenosis if a child presents with recurrent or prolonged croup. Perform bronchoscopy, CT, or MRI to confirm the diagnosis. The stenotic portion can be removed or stented, depending on the circumstances.

Tracheomalacia and Bronchomalacia

Tracheomalacia produces collapse of the trachea severe enough to cause airway obstruction. Bronchomalacia is the same disorder in the bronchi. Tracheobronchomalacia is the condition in both. Tracheobronchomalacia is usually mild and self-limited and does not require specific therapy. It can be secondary to other disorders such as tracheoesophageal fistula, cardiac abnormalities, or cervical/mediastinal masses.

LOBAR EMPHYSEMA AND OVERINFLATION

Congenital lobar emphysema can cause severe respiratory distress in the neonatal period, or onset of distress may be delayed up to 5–6 months. In this condition, one or more lobes are markedly enlarged with fluid or air. The left upper lobe is most commonly involved. The enlarged lobe pushes the diaphragm downward and the mediastinum to the opposite side. For infants with lobar

QuickQuiz

- What is the most common congenital anomaly of the nose?
- What is CHARGE syndrome?
- How is "tongue-tie" usually managed?
- What is the significance of thyroglossal duct cysts?
- What is the most common cause of stridor in the newborn?
- Which chromosomal abnormality is associated with the presence of glottic webs?
- How does tracheal stenosis present?
- What is Scimitar syndrome?

emphysema, this can be due to abnormalities of bronchial cartilage, and there is an increased risk of bronchial vessel compression by cysts.

Infants can present with tachypnea or grunting soon after birth. Physical examination may show increased resonance, diminished breath sounds, and expiratory wheezing. Because of the mediastinal shift, the heart sounds and trachea are also shifted on examination. Manage with oxygen and a short course of mechanical ventilation (if needed). Severe cases may require lobectomy.

PULMONARY HYPOPLASIA

Pulmonary hypoplasia is a common cause of neonatal death. Infants present at birth with respiratory distress and have severe hypoxemia and hypercarbia. Lung development is a complicated multifactorial process, and, if something in this process is disturbed, development can be severely affected. Pulmonary hypoplasia is commonly associated with premature rupture of membranes, which leads to premature delivery. This causes delivery of an infant with variable lung function. The hypoplasia can be due to a decrease in the number of alveoli or a decrease in the number of airway "generations."

Prognosis depends on the severity of the pulmonary hypoplasia and the associated anomalies that commonly coexist with or induce pulmonary hypoplasia. In severe cases, the lungs are too small and the infant dies. In less severe cases, the child may be kept alive on mechanical ventilation or extracorporeal membrane oxygenation (ECMO) until adequate lung growth occurs. Interestingly, some infants who appear to have markedly severe pulmonary hypoplasia improve dramatically within hours of being placed on mechanical ventilation.

SCIMITAR SYNDROME

Scimitar syndrome is a rare disorder in which the pulmonary venous blood from all or part of the right lung returns to the inferior vena cava (IVC) just above or below the diaphragm. There is an adult form, which consists of a small shunt between the right pulmonary veins and the IVC, and an infantile form, which consists of a large shunt between the anomalous arteries to the right lower lung and the IVC. The "adult form" doesn't appear clinically until after infancy and has a good prognosis. The infantile form presents with neonatal respiratory distress and heart failure, and mortality is high.

PULMONARY ARTERIOVENOUS FISTULAS

Pulmonary arteriovenous fistulas occur with several distinct congenital disorders. The most common cause (70%) is autosomal dominant hemorrhagic telangiectasia (Rendu-Osler-Weber syndrome). Bleeding occurs and can present at any age. By age 20, 50% of patients have had episodes of epistaxis. About 20% of patients with hereditary hemorrhagic telangiectasia develop pulmonary arteriovenous fistulas.

These fistulas are bad because there is right-to-left shunting of systemic venous blood directly into the pulmonary veins and left heart. Those affected present with dyspnea, hemoptysis, and exercise intolerance. Congestive heart failure (CHF) is very uncommon, though, because the blood flow is a "low pressure" system. Brain abscesses occur. Because of the persistent hypoxia, polycythemia is very common, and thrombosis/embolism is a concern.

Treat symptomatic patients with pulmonary angiography and ablation of the fistulas. You may need to surgically remove the fistulas if they are large or if ablation is unsuccessful.

PULMONARY SEQUESTRATIONS

Pulmonary sequestrations are essentially areas of the lung that are nonfunctional blobs of lung-like tissue. OK, a more scientific definition: Pulmonary sequestrations are areas of abnormal, nonfunctioning lung tissue that are embryonic and cystic. Pulmonary sequestrations can be either intralobar (contained within the normal visceral pleura) or extralobar (have their own separate pleura and venous drainage).

The intralobar form usually occurs in the lower lobes of each lung, but it also can occur in ectopic areas below the diaphragm. Anomalous vessels off the aorta supply the intralobar sequestrations, and the sequestrations drain through the pulmonary veins. The intralobar form is usually isolated and is typically identified during childhood or adolescence.

The extralobar form occurs most commonly in boys and is located just above or below the diaphragm, with almost all cases being on the left side. These sequestrations are supplied by pulmonary or systemic artery branches and drain into a systemic vein. The sequestration communicates frequently with the foregut, and other anomalies are common, including colon duplication, vertebrae abnormalities, and diaphragmatic defects. Infants can present with signs/symptoms of respiratory distress, and almost all cases are diagnosed before the age of 2 years.

Besides respiratory distress, you may see recurrent pneumonia, hemoptysis, or signs of infection. Older children will complain of severe pleuritic chest pain out of proportion to other findings.

CXR is usually abnormal. You also can order a CT scan and a Doppler ultrasound. Bronchoscopy will not be helpful because the sequestration is not connected to the normal airways. Surgically remove sequestrations.

BRONCHOGENIC CYSTS

Bronchogenic cysts result from abnormal budding of the tracheal diverticulum of the foregut before 16-weeks gestation. The cyst can be an isolated incidental finding on a CXR or may cause significant symptoms because of compression of surrounding tissues. They may also be prone to infection. Fever, chest pain, and productive cough are the most common presenting symptoms. Most bronchogenic cysts present as solitary and filled with mucus. They can occur in the paratracheal area, carinal area, hilar area, or paraesophageal area. The paraesophageal cyst does not communicate with the tracheobronchial tree but instead communicates with the esophagus.

If the cyst ruptures, pneumothorax or hemoptysis can occur. Order a CT or an MRI to define the diagnosis. Cyst excision is the preferred treatment because it is likely that symptoms and the potential for serious illness, such as malignancy, will develop.

NON-CONGENITAL DISORDERS OF THE NOSE

FOREIGN BODY

The nose is the toddler's playground. Various items can end up there without anyone's knowledge as to how they got there. These include crayons, various foods, toys, erasers, paper, beads, beans, stones, pencils. Suspect foreign body when a child presents with a unilateral nasal discharge. Over time, the drainage (and the child) becomes foul smelling.

Frequently, you can see the foreign material with good lighting and an otoscope or nasal speculum. Do not push the foreign body further into the nose.

Outpatient treatment includes topical anesthetics and forceps or nasal suction. In some cases, general anesthesia is required.

EPISTAXIS

Epistaxis (nose bleed) is common in children. The most common etiology is "nose picking." Nose bleeds occur most commonly during the dry, winter months. Besides nose picking, other causes include trauma (during sports, particularly), foreign bodies, and neoplasms (nasopharyngeal carcinoma, rhabdomyosarcomas, and lymphomas) of the nose. Cocaine abuse is a common mucosal irritant in those who use it and can result in epistaxis. So on the Board exam, question any adolescent with epistaxis about drug use. Coagulopathies can obviously predispose to prolonged epistaxis.

Most bleeding originates from the Kiesselbach plexus, and therapy involves pinching the nose for 5–10 minutes at the tip. This applies pressure to the Kiesselbach plexus. If bleeding is not abated, you may need to try other therapies, including decongestant sprays and cauterizing the bleeding site with silver nitrate in the outpatient setting. If bleeding still persists, refer the patient to an ENT specialist for nasal packing and observation.

Search for other underlying conditions if epistaxis continues to recur or is difficult to correct. In these cases, you will need to order coagulation and hematologic studies. Also, fully evaluate the nasal passages and look for nasal masses or other causes of epistaxis.

NASAL POLYPS

Nasal polyps are benign tumors that form in the nasal passages and are usually due to chronically inflamed nasal mucosa (Image 13-3). The most common cause in children is cystic fibrosis (CF). With any child younger than 12 years of age who has nasal polyps, evaluate for cystic fibrosis—even in the absence of other findings for CF. Other predisposing conditions include chronic sinusitis and allergic rhinitis. Note: There is also an "aspirin triad" associating nasal polyps, asthma, and aspirin sensitivity.

Kids with nasal polyps present with mouth breathing and nasal voices. Polyps look like gray, grape-like masses and occur between the nasal turbinates and septum.

Nasal decongestants are not usually very effective in decreasing polyp size. Nasal steroids, however, have been shown

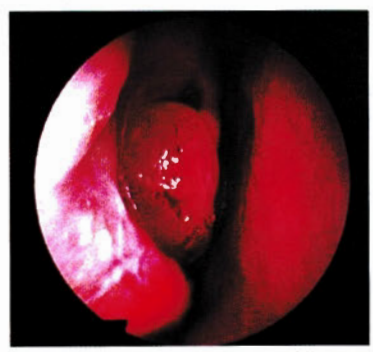


Image 13-3: Nasal Polyp

QuickQuiz

- Why is bronchoscopy not useful in diagnosing pulmonary sequestrations?
- What should you suspect in a child who presents with a unilateral, foul-smelling nasal discharge?
- What is the most common etiology for epistaxis?
- An adolescent with epistaxis should be asked about what type of illicit drug usage?
- What studies should be done in a child with recurrent or severe epistaxis?
- If you find nasal polyps in a child under the age of 12, what diagnosis should you consider first?
- What is the "aspirin triad"?
- What is an effective treatment of nasal polyps?
- What degree of thoracic curvature in scoliosis may result in respiratory symptoms?
- What is pectus excavatum?
- What is pectus carinatum?

to be quite effective for many polyps, especially in children with cystic fibrosis. You may need to surgically remove polyps if the nose is obstructed or deformed. In children with cystic fibrosis, the polyps can return after surgery.

CHEST WALL AND RESPIRATORY MUSCLE DISEASES

CHEST WALL MALFORMATIONS

Kyphoscoliosis (Scoliosis)

Kyphosis refers to how the spine is angled in the anterior-posterior direction, while scoliosis refers to how the spine is angled in the lateral direction. Most cases of scoliosis are idiopathic, with the remainder due to neuromuscular diseases or congenital rib/vertebral anomalies. Scoliosis results in abnormal positioning of the ribs, which in turn results in abnormal formation of the chest cavity. If scoliosis is severe, respiratory abnormalities can occur, including restrictive lung disease and/or distortion of large pulmonary vessels. Cardiopulmonary compromise generally occurs if scoliosis exceeds 90 degrees or more.

Table 13-1: Idiopathic Scoliosis Divided into 3 Categories

Age	Type	Sex Predilection
0–3 years	Infantile	Boys > Girls
3–10 years	Juvenile	Girls > Boys
> 10 years	Adolescent	Girls > Boys

Idiopathic scoliosis is divided into 3 categories (Table 13-1). About 3% of the population has a scoliotic curve of 10° or more and 0.5% has a curve of 20° or more. Scoliosis doubles death rates, sometimes occurring in the 4th to 5th decades due to cardiopulmonary insufficiency.

Mild scoliosis is asymptomatic, but when the thoracic curve exceeds 50°, you may find pulmonary function abnormalities. Alveolar hypoventilation is common.

Ideally, you will diagnose scoliosis early in childhood. If found, bracing will usually correct the problem. Surgical intervention is often required when the cause for scoliosis is neuromuscular weakness.

Pectus Excavatum

Pectus excavatum (funnel chest) is a depression of the midsternum (Image 13-4). It can occur as a congenital condition and be familial or acquired. By itself, pectus excavatum rarely causes respiratory or cardiac problems. More severe pectus can shift the heart leftward. Spirometry is usually normal.

Consider surgery on those who also have an associated thoracic scoliosis. Many have elective surgery to improve the aesthetic appearance of the chest.

Pectus Carinatum (Pigeon Breast)

Pectus carinatum is the "sticking out" of the sternum with the lateral depression of the costal cartilages (Image 13-5). Pectus carinatum is rarely symptomatic. Surgical repair is done mainly for cosmetic effect.

Jeune Syndrome (Asphyxiating Thoracic Dystrophy)

Jeune syndrome is an autosomal recessive disorder that presents with short ribs, a small rib cage, and renal disease. Some children also have short-limb dwarfism, pelvic anomalies, polydactyly, and hepatic involvement.

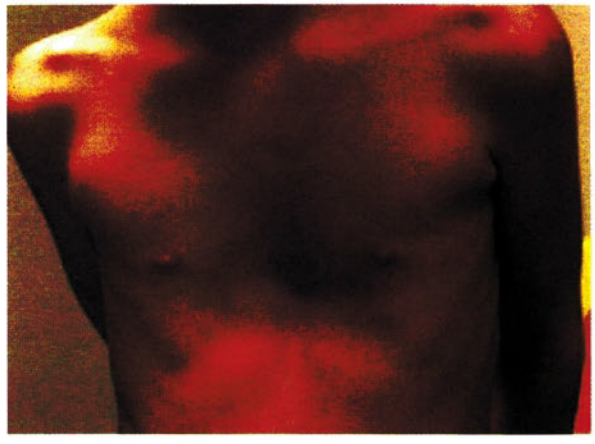


Image 13-4: Pectus Excavatum

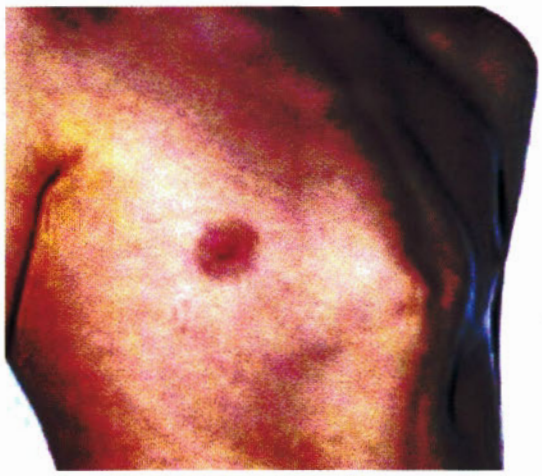


Image 13-5: Pectus Carinatum

Because of the short rib cage, restrictive lung disease is common. Respiratory failure is common, with infections largely responsible for morbidity and mortality.

NEUROMUSCULAR DISEASES

Spinal Muscular Atrophy

Spinal muscular atrophy (SMA) is the 2nd most common lethal autosomal recessive disorder! (CF is #1.) The gene is located on chromosome 5q. Patients with spinal muscular atrophy present with hypotonia, muscle atrophy and fasciculations, and weakness of the intracostal muscles. The lesion responsible is the degeneration of the anterior horn cell and, sometimes, the bulbar nuclei as well. Muscle weakness is symmetric, with the proximal muscles affected to a greater degree. The legs are more commonly affected than the arms. Because this affects only the motor anterior horn cell, you will not see sensory or intellectual deficits.

There are 4 types of SMA (but only 3 are diagnosed in pediatric patients):

- Type 1: Werdnig-Hoffmann, or severe infantile SMA. The most severe and presents before 6 months of age with hypotonia and weakness, difficulty feeding, and tongue fasciculations. Most patients die by 2 years of age due to respiratory failure.
- Type 2: Intermediate or chronic infantile SMA, occurs in up to 1/15,000 live births. Children are "normal" at birth and achieve initial normal milestones, but these are lost by 2 years of age. The majority die by the age of 12 years. Weakness can be static for long periods and then progress with intercurrent illness.
- Type 3: Kugelberg-Welander, or mild SMA, presents between ages 2 and 17 years. With this type, the child becomes unable to walk or stand unaided.
- Type 4: Presents later in the 2nd or 3rd decade and is otherwise like type 3.

Outcomes in type 3 and type 4 depend more on severity at presentation rather than age of presentation.

Today, 95% of cases can be diagnosed with gene mutation screening. The defect is the *SMN1* gene found on 5q13. CPK is normal. Manage with aggressive respiratory, nutritional, and orthopedic interventions. Before respiratory failure occurs, discuss the options of tracheostomy and lifelong mechanical ventilation with the family, in consultation with experts in the field.

Duchenne Muscular Dystrophy

Duchenne muscular dystrophy is the most common form of muscular dystrophy in childhood. It occurs in ~ 1/3,000 male births and is an X-linked recessive disorder. Duchenne's is caused by a mutation in the dystrophin gene and results in absent or deficient dystrophin protein.

Boys present between 2 and 6 years of age with frequent falling, a "waddling" gait, and toe walking. Classic things to look for on the Board exam: a child with calf muscle pseudohypertrophy and the Gowers sign—"climbing up the legs" using the hands when rising from a seated position on the floor (pushing against the shins, then knees, and finally the thighs). CPK is elevated. Affected boys generally lose the ability to walk by 11 years of age. Respiratory muscle weakness corresponds to gross motor weakness. Eventually, secretions cannot be handled, and aspiration/infection commonly occurs. Cardiomyopathy is also a component of Duchenne's.

Diagnosis is made by either muscle biopsy, which will show missing or deficient dystrophin, or gene testing.

Management is supportive. Scoliosis begins before loss of muscle function and progresses rapidly once the child is in a wheelchair. Long-term care is an important issue, and respiratory failure is a common cause of death. There is evidence to support the use of prednisone to improve muscle strength and respiratory function.

Myasthenia Gravis

Myasthenia gravis is rare in children but still is the most common primary disorder of neuromuscular transmission. In this disease, the postsynaptic receptors for acetylcholine are reduced in number, resulting in the postjunctional membrane being less sensitive to acetylcholine. The vast majority of patients who develop myasthenia in adolescence have autoantibodies that play a pathogenetically important role by attacking the acetylcholine receptor (AChR), fixing complement, and reducing the number of AChRs over time. These autoantibodies are thought to originate in hyperplastic germinal centers in the thymus where myoid cells expressing AChR are clustered.

Neonatal myasthenia gravis occurs when the newborn is exposed to transplacental passage of maternal acetylcholine receptor antibodies. The neonate usually presents within a few hours of birth (72 hours at the latest) with hypotonia, weak cry, difficulty feeding, facial weakness, and palpebral ptosis. Respiratory compromise occurs due to aspiration and progressive respiratory muscle

QuickQuiz

- Describe Werdnig-Hoffmann syndrome.
- Is CPK elevated in patients with spinal muscular atrophy syndromes?
- How is Duchenne muscular dystrophy transmitted?
- What is the mutation in Duchenne muscular dystrophy?
- What is Gowers sign?
- Is the CPK elevated in patients with Duchenne muscular dystrophy?
- With what receptors do the circulating autoantibodies react in children with juvenile myasthenia gravis?
- How does juvenile myasthenia gravis differ from congenital myasthenia gravis? From neonatal?
- What is the Tensilon maneuver?
- Removal of which tissue may result in remission in myasthenia gravis?
- Does secondhand smoke increase the risk of having a URI?
- Which viruses most commonly cause URIs?

weakness. Neonatal myasthenia resolves in 2–12 weeks after the maternal antibodies have cleared.

Congenital myasthenia gravis is an autosomal recessive disorder with variable age in onset. Those affected do not have circulating antibodies to the acetylcholine receptor.

Juvenile myasthenia gravis is an acquired autoimmune disorder and more often affects girls, usually after the age of 10 years. 80–90% of affected children have circulating autoantibodies to acetylcholine receptors. The disease progresses gradually, with worsening muscle weakness and respiratory compromise. Muscle weakness is exacerbated by repetitive muscle use. Ocular muscles are involved.

Classically we diagnosed myasthenia gravis by the following (Tensilon®) maneuver: Give anticholinesterase medication, such as edrophonium (Tensilon®), and look for transient improvement. Today this has been superseded by looking for specific autoantibodies directed at the acetylcholine receptor (AChR-Ab) or against a receptor-associated protein, muscle-specific tyrosine kinase (MuSK-Ab). One of these autoantibodies is found in 88–94% of those with myasthenia gravis. (Note: The Tensilon maneuver is useful in those with negative autoantibodies or only ocular involvement—this subgroup with only ocular involvement commonly won't have autoantibodies detected.) Today many experts use neostigmine instead.

Treat with oral anticholinesterase medications (neostigmine); these can increase the concentration of acetylcholine at the receptor site. Immunosuppression can be beneficial as well. Thymectomy may induce remission in as much as 50–60% of cases. Finally, plasmapheresis is beneficial for short-term amelioration of worsening symptoms.

DIAPHRAGM MALFORMATIONS

Eventration

Eventration is a marked elevation of the diaphragm. It is almost always congenital but can be acquired with a phrenic nerve injury. It is more common in boys and more commonly affects the left diaphragm. Infants can be asymptomatic or have tachypnea, dyspnea, retractions, and cyanosis. Physical examination will show unilateral decrease in breath sounds. CXR may show the defect, or fluoroscopy will show paradoxic movement of the diaphragm.

Accessory Diaphragm

Accessory diaphragm is rare and occurs when a fibromuscular band divides a hemithorax into two parts (the right side is more commonly affected). In most patients, it results in hypoplasia of the lung on the affected side, with resulting respiratory distress in the neonate. In older children, you will see recurrent infections. Lateral x-ray will show the accessory diaphragm. If it is symptomatic, surgically remove the accessory diaphragm.

INFECTIONS OF THE NOSE, PHARYNX, AND UPPER RESPIRATORY TRACT

UPPER RESPIRATORY INFECTIONS (URIs) OR COLDS

Upper respiratory infections are the most commonly occurring illnesses in children. Most children have between 3 and 8 colds a year, most often in the fall and winter months. Certain factors increase a child's risk for developing a cold: attending day care, inhaling secondhand smoke (or actively smoking), lower socioeconomic status, and conditions that result in overcrowding.

Viruses cause the majority of URIs. Rhinovirus makes up nearly 33% of cases, followed by coronavirus, adenovirus, and coxsackievirus. Once you get a virus and develop immunity, it is a lifelong immunity to that serotype. The problem is that each virus has potentially hundreds of other serotypes to which immunity is not conferred. Some viruses that cause URIs can spread to the lower respiratory tract, most notably the parainfluenza virus and respiratory syncytial virus (RSV).

URI viruses clinically present with low-grade fever and malaise, with upper respiratory symptoms of runny nose, cough, and congestion. Viruses that cause URIs rarely cause acute bloodstream infection or viremia. Shedding

of virus peaks at 2–7 days after initial symptoms and can last as long as 2 weeks.

Viruses that cause URIs can be transmitted in 3 ways:

1) Large-particle droplets, which can travel through coughing or sneezing and spread to another person
2) Small-particle aerosols, which travel longer distances and can directly enter the alveoli
3) Secretions on hands or other surfaces (fomites), which can transmit the virus by direct physical contact (The recipients inoculate themselves by touching their nose or other mucous membrane with their contaminated hands/fingers.)

Do not order laboratory tests in children with URIs. Perform a careful history and physical examination. Obviously, you will need further studies if the diagnosis is not clear or if history/physical is incompatible with a diagnosis of URI.

The most common complication of a common cold is otitis media. Other complications can include sinusitis, asthma exacerbation, and pneumonia. Thick, "green" nasal discharge by itself in the first few days of a URI does not mean the patient has sinusitis; it usually signifies an increase in the number of inflammatory cells present to help fight off the infection.

Treat symptoms, most often with acetaminophen and decongestants. Many recommend no treatment at all since no pharmacologic therapy has been shown to reduce the duration of a URI. Additionally, for children younger than 2 years, certain medications (pseudoephedrine, carbinoxamine, and dextromethorphan) have been associated with deaths in recent years. Thus, many suggest that antitussives and decongestants not be used for relief of cold symptoms in children younger than 2 years of age. Instead try saline nose drops with a gentle bulb syringe to loosen secretions. Antihistamines are also not recommended for most children because they decrease cilia movement and can delay mucus clearance. Some recommend guaifenesin, a mucolytic agent, to thin secretions and improve ciliary function. Topical decongestants can relieve nasal congestion in older children; however, limit them to short time periods because of the risks of rebound congestion, tachyphylaxes, and rhinitis medicamentosa.

Use of multivitamins, vitamin C, echinacea, and zinc have not been shown to be beneficial in children or adults. Chicken soup as therapy has not been adequately studied in children.

SINUSITIS

People generally think of sinusitis as bacterial, but almost all cases of viral rhinitis result in viral rhinosinusitis. It is frequently difficult to differentiate between the two.

Remember how the sinuses develop: The maxillary and ethmoid sinuses are anatomically present *in utero*. Frontal and sphenoid sinuses begin to develop by 1–2 years of age but are not radiographically seen until 5–8 years of age.

The common bacterial causes of acute sinusitis are *Streptococcus pneumoniae*, *Moraxella catarrhalis*, and nontypeable *Haemophilus influenzae*. With chronic sinusitis (symptoms more than 30 days), you may find *Staphylococcus aureus*, α-hemolytic streptococci, and anaerobes.

Clinically, children with sinusitis present most commonly with cough and nasal discharge. The more "adult-like" presentation is seen in adolescents and includes facial pain, tenderness, and facial edema. In children, cough is bad in the daytime and worsens with supine position. Nasal discharge can be clear or green. Sore throat is common from postnasal drainage. Fever occurs more commonly in older children.

One clue is the duration of symptoms. Most URIs will improve in 7–10 days. Suspect bacterial sinusitis when symptoms last longer than this. Occasionally, severe sinusitis will occur in the initial 7 days of the illness, but these children will typically have high fever and headache.

Sinus x-rays and CT scans are controversial (Image 13-6). The AAP recommends that for children ≤ 6 years of age who have persistent respiratory symptoms that have not improved for > 10 but < 30 days, the diagnosis of acute bacterial sinusitis can be made on clinical criteria without imaging. For those children > 6 years of age, the AAP is non-committal on the need for imaging to confirm the diagnosis of sinusitis. However, the American College of Radiology and the Sinus and Allergy Health partnership (an ENT group) recommend not imaging for the diagnosis of acute uncomplicated sinusitis. Mucosal thickening, air-fluid levels, and sinus opacification can be due just as easily to a virus as to

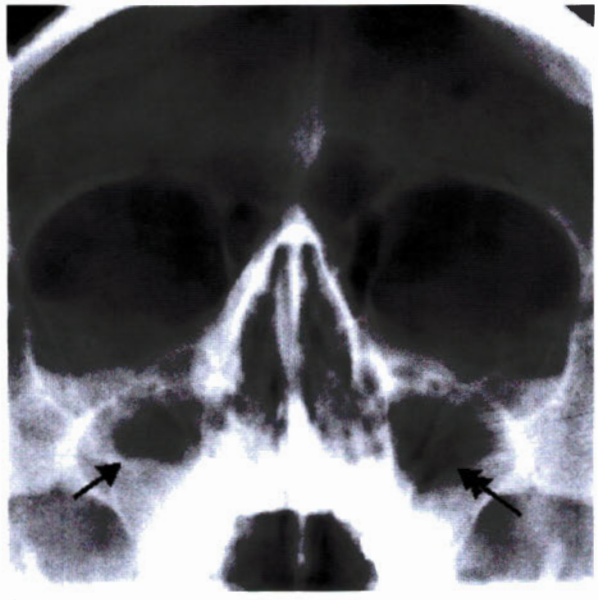


Image 13-6: Acute Sinusitis

QuickQuiz

- What laboratory testing is necessary in most URIs?
- Does green nasal discharge in the first few days of a URI indicate that sinusitis is likely?
- Are antihistamines recommended in the therapy for URIs in children?
- Which sinuses are present at birth?
- If a child presents at day 9 during a URI with new fever, worsening nighttime cough, and sore throat, what should you suspect?
- A child with severe immunosuppression presents with suspected sinus infection. What is the best way to diagnose the infection and treat appropriately?
- What is Pott's puffy tumor?
- In a diabetic adolescent with uncontrolled serum glucose and the finding of a black eschar in the nose, what organism should be suspected?
- What is the most common cause of acute pharyngitis in children?
- In an older child, is a sore throat accompanied by conjunctivitis, runny nose, or hoarseness likely to be due to *S. pyogenes*?

bacteria. Nasal swab cultures are worthless. The only method for getting valid bacterial cultures is by aspirating the sinus by direct antral puncture; however, reserve this only for those who have life-threatening illness, are immunocompromised, or have illness that is unresponsive to therapy.

Treatment is aimed at the most common etiologies. Most centers still recommend amoxicillin; however, many use amoxicillin with clavulanic acid, extended-spectrum macrolides, or 2nd and 3rd generation cephalosporins due to the increasing rate of β-lactamase production by *H. influenzae* and *M. catarrhalis*. *S. pneumoniae* resistance rates to amoxicillin and trimethoprim/sulfamethoxazole have risen dramatically, leading many to use high-dose amoxicillin (80–100 mg/kg/day) for therapy. Treatment duration is controversial: Some recommend 10–14 days total, while others recommend therapy for 14–21 days or until symptoms have resolved for at least 7 days.

Complications of sinusitis can be quite serious. Orbital cellulitis (Image 13-7) or abscess formation can occur. Osteomyelitis can also occur from contiguous spread. When an abscess and/or osteomyelitis occur over the frontal sinus, this is called "Pott's puffy tumor." Meningitis and epidural abscesses have been reported. For any of these complications, order a CT scan and hospital admission.

Unusual organisms can cause sinusitis, depending on underlying conditions. In children with prolonged neutropenia due to chemotherapy, the risk of *Aspergillus* or *Candida* sinusitis is increased. Mucormycosis is a serious life-threatening disease that occurs in poorly controlled diabetes and may present as a black eschar on the nasal turbinate. It is dangerous because it frequently likes to "grow backward" into the bone and brain.

ACUTE PHARYNGITIS

Acute pharyngitis peaks between the ages of 4 and 7 years in children and is rare in children under 1 year of age. The most common cause of acute pharyngitis is viruses. *Streptococcus pyogenes* (group A streptococcus: GAS) is the most common bacterial etiology but makes up only 15% of cases of pharyngitis! Other less common causes include *Mycoplasma* and *Arcanobacterium haemolyticum*. Don't forget: In the case of sexually active adolescents, also consider *Neisseria gonorrhea*. Diphtheria is discussed in the Infectious Disease section. You can culture other bacteria during a viral infection, but rarely, if ever, are they the etiology of the pharyngitis.

Clinically, it is very difficult to differentiate between viral and streptococcal pharyngitis in children. Generally, viral pharyngitis has a more gradual onset with fever, malaise, and moderate throat pain. Look for accompanying symptoms, such as conjunctivitis, rhinitis, cough, hoarseness, coryza, ulcerative lesions, or viral rashes, to help discern a virus as the etiology. Exudates can occur in both and usually are indistinguishable. Typically, viral pharyngitis lasts less than 2 days and rarely exceeds 5 days in duration. By contrast, streptococcal pharyngitis frequently begins with nonspecific complaints of headache, abdominal pain, or vomiting. Fever is usually quite high. After these initial symptoms, the child develops a sore throat.

Classically, children will have exudates, pharyngeal redness, and enlarged tonsils. Tender, enlarged anterior cervical lymph nodes are common. Fever can last 1–4 days.

For *Streptococcus pyogenes*, the most helpful clues are finding diffuse erythema of the tonsils and tonsillar pillars, petechiae of the soft palate, and absence of URI symptoms.

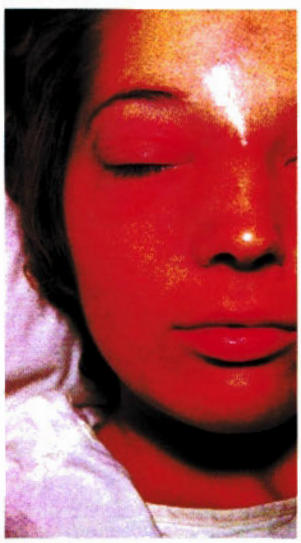


Image 13-7: Orbital Cellulitis

In children less than 2 years of age, be familiar with this clinical presentation: coryza with postnasal discharge, fever (can last up to 8 weeks), pharyngitis, poor appetite, and tender cervical lymphadenitis. This is called streptococcosis and is a persistent illness in these younger children.

Diagnose with rapid detection methods of optical immunoassay and chemiluminescent DNA probes. The AAP recommends following up with a throat culture if the rapid test is negative.

Be most concerned with the 2 complications of *S. pyogenes* infection:

1) Rheumatic fever (RF), which can be prevented if therapy is given within the first 9 days after onset of symptoms (Remember it has to be pharyngeal strains for RF!)
2) Post-streptococcal glomerulonephritis, which can occur regardless of therapy—and can be pharyngeal, skin, or other locations for this to occur

Treat with penicillin 250 mg bid to tid orally for children < 60 lbs and 500 mg bid to tid for heavier children. Use IM injections (penicillin G benzathine 600,000 U for children < 27 kg and 1.2 million U for children ≥ 27 kg) when adherence is a concern or if the child is vomiting. Children respond with defervescence within 24 hours of therapy, and penicillin shortens the disease course by 1.5 days on average. Once-daily amoxicillin (750 mg x 10 days) has also been shown to be effective. Use erythromycin, clindamycin, or azithromycin for those allergic to penicillin.

A common question: How soon can children go back to school? In other words, when are they no longer infectious? The answer is: The child becomes noninfectious within a few hours after penicillin therapy; so, many allow the child to return to school or day care the next day if clinically improved.

Recurrence can occur and can be retreated with the same antimicrobial agent, an alternative oral drug, or an IM dose of penicillin G (especially if nonadherence to oral therapy was likely). The 2009 Red Book does not recommend any of these agents as more appropriate in this setting.

Chronic Carriers of GAS

Chronic pharyngeal carriage of group A streptococcus (GAS) occurs, and in general, antimicrobial therapy is not indicated for most carriers. However, according to the 2009 Red Book there are exceptions that should be considered for treatment of carriers:

- In the setting of an outbreak of acute rheumatic fever or PSGN (post-streptococcal glomerulonephritis)
- Outbreak of GAS in a semi-closed community (e.g., dorm, juvenile jail)
- Family history of RF
- Multiple episodes of documented symptomatic GAS in a family during a period of many weeks despite appropriate therapy

The most effective therapy for eradicating chronic carriers has been clindamycin 20 mg/kg/day in 3 divided doses for 10 days. Other agents include amoxicillin-clavulanate or azithromycin; also, the use of rifampin for the last 4 days of the usual penicillin therapy (oral or IM) has been effective in some refractory cases.

RETROPHARYNGEAL ABSCESS

Retropharyngeal abscess occurs as a complication in children with bacterial pharyngitis or can occur as an extension from a wound infection following a penetrating injury (e.g., pencil injury to the posterior pharynx). The most common causes are *S. pyogenes*, oral anaerobes (most commonly *Fusobacteria* or *Prevotella*), and *S. aureus*.

The child (most commonly affected are 2–4 years of age) presents with an abrupt onset of high fever and difficulty swallowing. This occurs during their "acute pharyngitis," and the child develops the following symptoms in the midst of the infection: refusal to eat, severe throat pain, hyperextension of the head, and gurgling respirations. Drooling soon develops. Most children have a "bulge" in the posterior pharyngeal wall. A lateral x-ray of the nasopharynx and neck with mild extension will show the mass; the retropharyngeal soft tissue will be more than 50% of the width of the adjacent vertebral body.

This is a medical emergency. Without treatment, rupture into the pharynx can result in aspiration of the pus, or the rupture can extend into fascial planes. Stridor can also occur, and it may simulate croup. You can order a CT scan to delineate the pathology.

In the pre-fluctuant phase, treatment with nafcillin for *S. aureus* and clindamycin for anaerobes may prevent suppuration. Some use single-agent therapy with ampicillin-sulbactam instead. Continue IV therapy until the patient is afebrile and clinically improved, and then complete therapy with oral amoxicillin-clavulanate or clindamycin to provide a total of 14 days of therapy. If the abscess is fluctuant, drainage is necessary.

PERITONSILLAR ABSCESS

Peritonsillar abscess is almost always due to group A streptococcus, oral anaerobes, or *Staphylococcus aureus*. The abscess occurs after or with an acute pharyngotonsillitis. Fever can abate for several days and then recur, or it may be continuous. The temperature can be as high as 105° F. The patient presents with severe pain and trismus and refuses to speak or swallow. A "hot potato"

Quick Quiz

- Same question as previous, but now in a 1-year-old and add the findings of cervical lymphadenitis and poor appetite.
- Does treatment with penicillin shorten the disease course in group A strep throat infections?
- Does treatment with penicillin prevent rheumatic fever in group A strep pharyngitis?
- How soon may a child return to school after being treated for group A strep pharyngitis?
- In retropharyngeal abscess, what will the lateral x-ray show?
- What type of voice is described with peritonsillar abscess?
- What are the indications for tonsillectomy?
- Does tonsillectomy help with chronic otitis media? Does adenoidectomy help?
- What virus causes most cases of croup?
- What is the treatment for croup?

voice is described. The uvula may be displaced to the opposite side.

Management is dependent on age and the cooperativeness of the child. For most without a history of sore throat or recurrent pharyngitis, simple incision and drainage is best done in the operating room. If there is a history of previous recurrent pharyngitis or a prior peritonsillar abscess, then a tonsillectomy is recommended. Treat with the same antibiotics as used for retropharyngeal abscess (see above). Surgery may be postponed for 12–24 hours pending response to antibiotics if there is no evidence of airway compromise, septicemia, severe trismus, or other complications. For those patients < 6 years of age, antibiotic therapy alone has been shown to be effective in one series.

CHRONIC TONSILLITIS

Indications for Tonsillectomy

- Recurrent pharyngitis (7 episodes in the past year, 5 in each of the last 2 years, or 3 in each of the past 3 years)
- Marked/severe adenotonsillar hypertrophy
- Exclude tumor
- Severe sleep apnea

Tonsillectomy does not help with preventing or treating acute or chronic sinusitis or chronic otitis media. Tonsillectomy does not help prevent URIs! Perform surgery 2–3 weeks after any uncomplicated infection has resolved.

CHRONIC ADENOIDAL HYPERTROPHY ("ADENOIDS")

Indications for Adenoidectomy

- Persistent mouth breathing
- Repeated or chronic otitis media with effusion
- Hyponasal speech
- Adenoid facies
- Persistent or recurrent nasopharyngitis when it seems to be temporally related to hypertrophied adenoid tissue

Do not perform a tonsillectomy for these above problems.

LARYNGOTRACHEOBRONCHITIS (CROUP)

Croup is a clinical diagnosis in which the child presents with a high-pitched, barking cough and inspiratory stridor. It most commonly occurs between the ages of 3 months and 3 years, with a peak around 2 years of age. Boys are more often affected than girls. Most incidents occur in fall and early winter. Almost all cases are due to parainfluenza virus, Types I and II. Sporadic cases can occur with other parainfluenza virus types, influenza virus, RSV, measles, and other viruses.

The virus usually causes subglottic airway narrowing at the cricoid cartilage, which results in the barking cough and stridor. Neck x-ray will frequently show subglottic narrowing (steeple sign, Image 13-8).

Croup is usually managed supportively with cool-mist vaporizers, using a shower to steam up the bathroom, or taking a child outside in the cool night air. If the child presents to the emergency department, most centers give 0.6 mg/kg (max 10 mg) of oral (if possible, if not then IM/IV) dexamethasone, which has been proven to decrease the length and severity of the illness.

For moderate stridor at rest, or moderate retractions, or more severe symptoms, most add aerosolized racemic epinephrine as 0.05 mL/kg/dose (max 0.5 mL) of a 2.25% solution diluted to 3 mL total volume normal saline via nebulizer with 100% oxygen. The main problem with this therapy is the "rebound phenomenon," with symptom recurrence after the medication has worn off. Therefore, observe children in the emergency department at least 3–4 hours after therapy has begun.

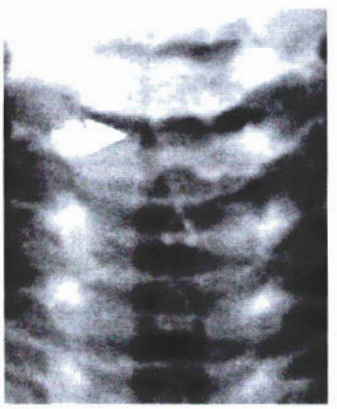


Image 13-8: Steeple Sign

Spasmodic croup is usually a noninfectious

croup in which the child wakes up in the middle of the night with symptoms of barking cough and mild-to-moderate stridor. The next day the child is healthy, but the cycle repeats itself that night and possibly again over 2–3 nights. It may or may not respond to cool mist or night air. Gastrointestinal reflux may be an important component. There may be mild signs of acute respiratory tract infection (coryza) but no fever; the child usually appears well otherwise.

EPIGLOTTITIS

Epiglottitis is an infection of the larynx with rapid swelling of the epiglottis and increasing respiratory distress. It is now rare due to *H. influenzae* vaccine. However, *H. influenzae* is still the most common cause, followed by *Streptococcus pneumoniae*, *Streptococcus pyogenes*, and *Staphylococcus aureus*.

Epiglottitis affects children between the ages of 2 and 5 years and presents with abrupt onset of fever, sore throat, drooling, and stridor. Frequently, the child will sit forward with the chin extended, and many children have that "I'm about to die" look.

Never use a tongue depressor on an uncooperative child in an outpatient setting in an attempt to visualize the oropharynx. You must examine the uncooperative patient emergently in controlled conditions (such as an OR), where a skilled anesthesiologist or ENT physician can provide an artificial airway. Findings of a cherry-red epiglottis are diagnostic (Image 13-9).

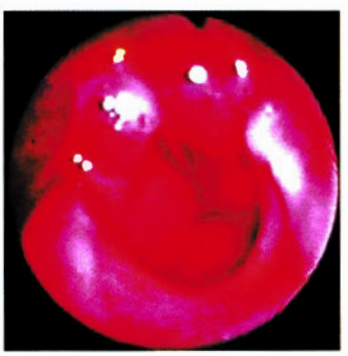


Image 13-9: Epiglottitis

Besides airway management, treatment must include antibiotics, which typically include an antistaphylococcal drug (oxacillin, cefazolin, or clindamycin) and either ceftriaxone or cefotaxime. Most of these children are bacteremic. If MRSA (methicillin-resistant *Staphylococcus aureus*) carriage is high in the community, many will use vancomycin as the antistaphylococcal agent.

BACTERIAL TRACHEITIS

Bacterial tracheitis is most commonly due to *Staphylococcus aureus*. It can also be caused by parainfluenza virus Type I, *Moraxella catarrhalis*, nontypeable *H. influenzae*, and anaerobes. Bacterial tracheitis usually follows a viral URI and does not involve the epiglottis. Because of the *H. influenzae* vaccine, bacterial tracheitis due to *S. aureus* is more common than epiglottitis.

The child is usually less than 3 years of age and presents with high fever and a brassy cough typical for croup; however, the stridor/croup does not respond to usual treatment measures for croup, and the child deteriorates rapidly. Intubation or tracheostomy is frequently required.

Treatment includes antibiotics, particularly nafcillin, aimed at *Staphylococcus aureus*. Patients respond to therapy within 2–3 days; however, due to the continued edema from the tracheitis, most patients require an average of 10–14 days of hospitalization. Vancomycin is used if MRSA is common in the community.

INFECTIONS OF THE LOWER RESPIRATORY TRACT

BRONCHIOLITIS

Bronchiolitis is very common in infants and young children, especially during the winter and spring. Those affected frequently have a prodrome of low-grade fever, runny nose, and poor feeding before progressing to cough and wheezing.

Bronchiolitis is most commonly due to respiratory syncytial virus (RSV), which is ubiquitous. Most infants are infectious for about 7 days, but some can have persistent shedding for months. Risk factors for severe RSV infection include secondhand smoke exposure, family history of asthma, crowded living conditions, and low birth weight. RSV can be spread by large-particle dispersion as well as through contact with fomites. Other etiologies include parainfluenza, human metapneumovirus (hMPV), influenza, rhinovirus, coronavirus, and bocavirus (HBoV).

Infants can be severely affected and may require mechanical ventilation, especially if they are premature. Look for wheezing, crackles, stridor, retractions, or cough. CXR shows hyperinflation and is nonspecific.

Treatment is supportive, and oxygen therapy is usually required for the hospitalized infant. β-agonist therapy may be beneficial but is not recommended by the 2009 Red Book for routine care in first-time wheezing. Corticosteroids are not recommended. Ribavirin was used in the past, but recent studies have shown little benefit.

The AAP has guidelines on RSV immunoprophylaxis for high-risk infants and children. Consider for:

- Infants and children < 24 months with chronic lung disease of prematurity who require medical therapy (e.g., diuretics, oxygen) within 6 months before the start of RSV season
- Infants born at < 32-weeks gestation depending on their gestational and chronological age at the start of RSV season; those born at 29–32 weeks benefit most up to 6 months of age

QuickQuiz

- What are the common causes of epiglottitis today?
- If you visualize a cherry-red epiglottis, what is your diagnosis?
- What is the treatment of epiglottitis?
- What organism most commonly causes bacterial tracheitis?
- What organism most commonly causes bronchiolitis?
- In children, what vital sign must usually be present to make the diagnosis of pneumonia?
- When should you get a CXR in a child?

- Infants born at < 28-weeks gestation during the first 12 months of life
- Children < 24 months of age with hemodynamically significant cyanotic and acyanotic congenital heart disease (but not secundum ASD, small VSD, pulmonic stenosis, uncomplicated aortic stenosis, PDA, mild coarctation, or those with more severe disease who have been corrected and no longer require medication)
- Those 32–35 weeks of age and with 1 of the following:
  - Attends day care
  - Infant has a sibling < 5 years of age

Once the child "qualifies" for initiation of prophylaxis at the start of the RSV season, prophylaxis should be continued based on month of birth and gestational age (a rather complicated table is published in the 2009 Red Book, which you will not be expected to know for the Board exam). The key is that more advanced gestational-age children (32–35 weeks) without underlying lung disease will receive anywhere from 0 to 3 doses, depending on their month of birth. Those < 28 weeks will generally receive 5 doses in their first RSV season as well as their 2nd season (i.e., these infants are at much greater risk than the older group).

PNEUMONIA—GENERAL CONSIDERATIONS

Pneumonia is a difficult topic, mainly because the definition lacks precision! You must first assess whether an infant or child actually has pneumonia. Clinical markers are not the same in infants and children as in adults, and the younger patients don't present with the typical fever, cough, and productive sputum. Thus, various clinical guidelines have been developed to help us sort this all out. The following information on diagnosing pneumonia refers to children older than 2 months of age. Infants younger than 2 months with pneumonia are discussed in The Fetus & Newborn section.

First, consider whether the child has signs of respiratory distress:

- Tachypnea
- Subcostal retractions
- Cough
- Crackles
- Decreased breath sounds

The positive predictive values of these signs are best if the child has fever, or cyanosis, and more than one of the signs.

Tachypnea alone has a sensitivity of about 70% and a specificity of only 40–70%. Furthermore, the positive predictive value of tachypnea falls to 20% in children 2 years of age or younger. Just what "number" defines tachypnea? The World Health Organization (WHO) has set up thresholds based on age (Table 13-2).

So using the guidelines, a 7-year-old with fever and respiratory rate of 30 is at risk for pneumonia.

Note that without the presence of fever, the negative predictive value is 97%. In other words, without fever, pneumonia is unlikely.

What about CXR?

CXR is recommended in the following:

- Children under 5 years of age with fever and high WBCs of unknown source.
- There is clinical evidence of possible pneumonia, but the clinical findings are not clear-cut.
- Pleural effusion is suspected.
- Pneumonia is unresponsive to antibiotics.

Most studies have shown that CXR cannot distinguish between viral and bacterial pneumonia, and many studies have failed to show that CXR actually alters management decisions. (See Image 13-10, Left Lower Lobe Pneumonia.)

What about WBC count and differentials?

Most data show that the likelihood of a bacterial cause increases as the WBC count increases above 15–20,000, and a bacterial etiology is especially likely with WBCs this high and a fever > 39° C (102.2° F). But when should you order a WBC count? Consider a WBC count when the information available to you is insufficient to determine if antibiotics should be used.

Table 13-2: Tachypnea Thresholds Based on Age—A Comparison

Age	Normal (breaths/min)	Tachypnea (breaths/min)
2–12 months	25–40	50
1–5 years	20–30	40
> 5 years	15–25	20

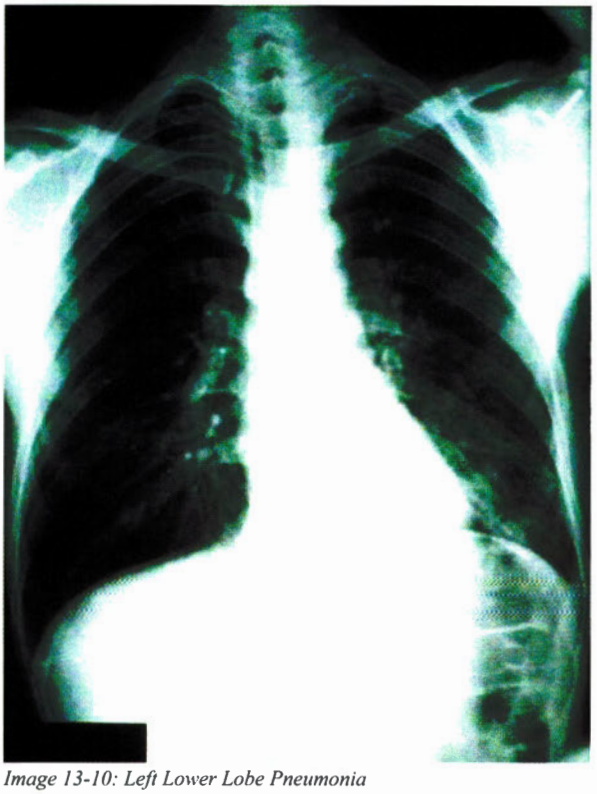


Image 13-10: Left Lower Lobe Pneumonia

Sputum Gram stains and cultures are very controversial. If possible, in a child with severe disease, obtain a high-quality specimen (< 10 squamous epithelial cells and > 25 WBCs/ low-power field). For mild or moderate disease, sputum studies are generally not necessary.

What about blood cultures?

They are not recommended as routine studies in the outpatient setting (the chance of a positive blood culture in this setting is < 5%), but they are recommended for inpatients with more severe pneumonia.

What about serologic testing, cultures, and PCR testing?

Testing for specific pathogens, such as *Mycoplasma pneumoniae* or *Chlamydia pneumoniae,* is not routinely recommended. Use other tests, such as viral cultures, viral antigens, and cold agglutinins, only when the result would alter therapy.

Use of ESR and C-reactive protein (CRP) is not recommended to diagnose pneumonia.

BACTERIAL PNEUMONIA

Streptococcus pneumoniae

Streptococcus pneumoniae classically presents as an abrupt infection with fever, chills, chest pain, and dyspnea, as well as blood-tinged sputum. (Remember pneumococci are gram-positive diplococci.) Children with pneumococcal pneumonia appear clinically ill and have tachypnea and tachycardia.

Physical examination shows dullness to percussion over the affected lung segment and diminished breath sounds. You also may detect pleural friction rubs. Frank crackles may not be heard until later in the course of the illness.

Pleural effusions are common and usually are sterile. (See Image 13-11—an AP CXR showing bilateral pneumonia and Image 13-12—a lateral decubitus x-ray showing layering.) Empyema is a late complication.

Poor prognostic findings are leukopenia and shock; if both are present, mortality may approach 50%.

Of major concern today is the emergence of penicillin-resistant pneumococci; in some centers, it approaches 40–50% of cases. For outpatient therapy, use high-dose amoxicillin (80–100 mg/kg/day) for 7–10 days. For children with vomiting who are still well enough to return home, ceftriaxone may be given; then follow up the next day with oral outpatient therapy. For inpatient therapy, most use a 2nd or 3rd generation cephalosporin. For those penicillin-allergic in either setting, you may consider a macrolide or cephalosporin (if no anaphylaxis to penicillin). Vancomycin can be used if macrolide resistance is high or if cephalosporins cannot be used. In children

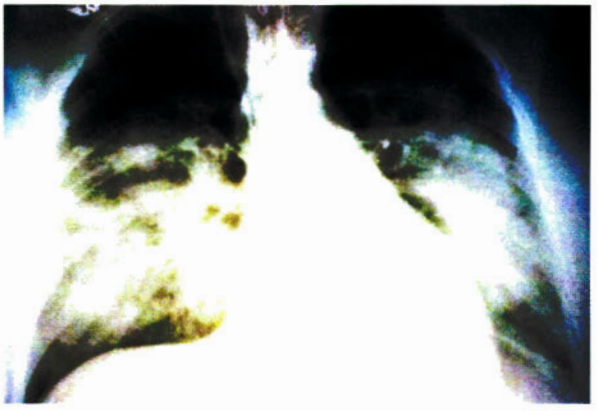


Image 13-11: Bilateral Pneumonia

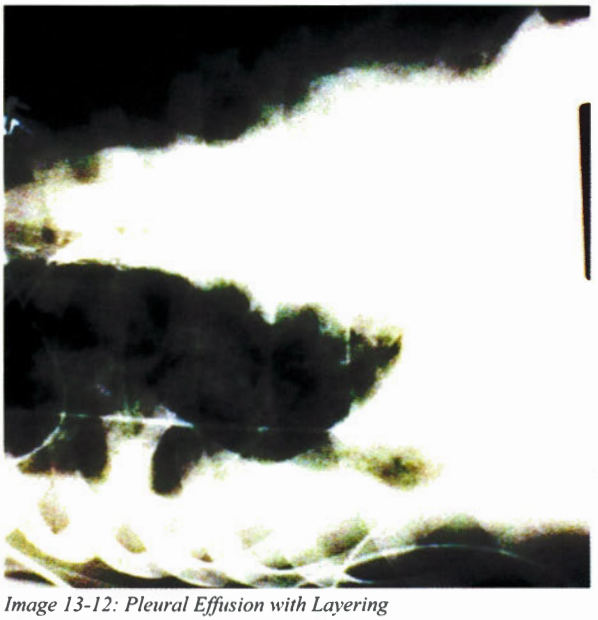


Image 13-12: Pleural Effusion with Layering

QuickQuiz

- Are blood cultures routinely recommended in the management of outpatient pneumonia in children?
- What serologic tests are routinely recommended in the management of outpatient pneumonia in children?
- Gram-positive diplococci seen in a sputum sample with a large number of PMNs and few epithelial cells indicate which most likely organism?
- What should you do about a persistent (1 week out now) pleural effusion in a child with recent pneumococcal pneumonia?
- What should you do about pneumatoceles if they occur in *S. pyogenes* pneumonia?
- A patient with influenza develops a bacterial pneumonia. Besides pneumococcus, what organism should you especially consider?
- Which antibiotic is commonly used for presumed anaerobic pneumonia?
- What does a CXR in a child with viral pneumonia commonly show?

with meningitis in addition to pneumonia, vancomycin and ceftriaxone are generally recommended until sensitivities return.

Pleural effusions may persist for weeks and resolve without specific therapy. Later, if the child has recurrence of fever or symptoms with a persistent pleural effusion, perform appropriate studies (thoracentesis with cell count, pH, protein, glucose) on the fluid to determine if empyema has occurred.

Streptococcus pyogenes (group A streptococcus)

Streptococcus pyogenes causes pneumonia usually after a rash disease, such as rubeola, varicella, or scarlet fever. It can also occur sporadically without prior illness. *S. pyogenes* pneumonia presents abruptly with fever, chest pain, cough, and leukocytosis. Physical findings are similar to pneumococcus. Pneumatoceles are common and disappear spontaneously. The most common complications from *S. pyogenes* pneumonia are abscesses and empyema. Treat outpatients with oral penicillin/amoxicillin for 10–14 days. For hospitalized children, treat with IV penicillin. If empyema has occurred, closed-suction drainage is usually necessary.

Haemophilus influenzae

Since *Haemophilus influenzae* vaccine use has become widespread, the incidence of this bacterium as a cause of pneumonia has decreased markedly. Findings are similar to pneumococcus, although it usually has a more insidious course. Outpatient therapy includes amoxicillin-clavulanate acid. Inpatient therapy is generally ceftriaxone or cefotaxime.

Staphylococcus aureus

Staphylococcus aureus is much less common than pneumococcus and *S. pyogenes*, but it is very serious and frequently a fulminant cause of pneumonia. Infants with staph pneumonia frequently develop pneumatoceles, pneumothoraces, abscesses, and empyema. The right lung is affected more often than the left.

Suspect this organism in a patient with a recent URI or influenza, who presents with abrupt onset of fever, tachypnea, tachycardia, and cyanosis. CXR showing distinct pneumatoceles is classic. Blood cultures are frequently positive.

Patients with staphylococcal pneumonia require hospitalization and quick treatment with nafcillin or vancomycin (if high prevalence of MRSA in the community or if the patient has had recent hospitalization, indwelling catheter, or tracheostomy).

Pneumothoraces require decompression. Pneumatoceles are very common and appear 3–4 days into therapy. They require no specific therapy and usually resolve over time. Empyema requires closed suction drainage.

Klebsiella pneumoniae

Klebsiella pneumoniae is a rare cause of pneumonia in children. When it occurs, it is typically in children with underlying immunosuppression or those who have had prolonged endotracheal intubation.

Anaerobes

Anaerobes are rare causes of pneumonia in children and occur mainly in those who are prone to aspirate oral secretions. Strong putrid sputum is characteristic; many times just walking into the room will give the diagnosis away! Clindamycin is commonly used for anaerobic pneumonias.

VIRAL PNEUMONIA

Pneumonia in children is most likely due to viruses. These include RSV, parainfluenza viruses, adenoviruses, rhinoviruses, influenza viruses, varicella virus, and rubeola virus. Clinically, children have a prodrome of URI-type symptoms, which is followed by a sudden onset of tachypnea, nonproductive and frequently paroxysmal cough, and low-grade fever. Physical findings may show dullness or decreased breath sounds. You may hear wheezing and crackles or, in other cases, the lung examination may be normal except for tachypnea. CXR usually will show perihilar and parenchymal infiltrates. Treatment is supportive, with fluids and

oxygen if necessary. Specific viruses are discussed in the Infectious Disease section.

FUNGAL INFECTIONS

Histoplasmosis

Histoplasmosis is common in endemic areas—southern and midwestern U.S. Histoplasmosis is especially seen in the Mississippi and Ohio River valleys (do not confuse this with "[San Joaquin] valley fever" below). Think of histoplasMOsis (Mississippi, Ohio). It is associated with soil animals (chickens) and cave-dwelling animals (bats). Most cases are asymptomatic, and a majority of residents in endemic areas have serologic evidence of past infection.

With acute disease, the chest x-ray shows hilar adenopathy and focal alveolar infiltrates. Heavy exposure ("epidemic," disseminating form) is suggested by a chest x-ray revealing multiple nodules in addition to the hilar adenopathy. No treatment is indicated for acute pulmonary disease without complications. Use itraconazole for persistent disease > 4 months or if hypoxia occurs in the acute setting. Disseminating disease requires amphotericin B.

Coccidioidomycosis

Coccidioides immitis infection (coccidioidomycosis) is endemic in the southwestern U.S. (C for California). The infection is also called "valley fever." Spores grow best in arid, desert-like climates—the term comes from the San Joaquin valley. Erythema nodosum and erythema multiforme commonly occur in infected people. A typical presentation is a person with erythema multiforme and a history of travel to the Southwest.

Diagnose with complement fixation titers.

The self-limited form usually does not require treatment and may leave thin-walled lung cavities. Treat with fluconazole and/or amphotericin B if there is either enlargement on chest x-ray or hemoptysis.

Disseminated coccidioidomycosis is seen in immunocompromised/HIV patients. This is a fulminant disease with meningitis and with skin and bone involvement. Even with treatment (amphotericin B), it is frequently fatal.

Blastomycosis

Blastomycosis is uncommon. It is usually acquired in the central, southeastern and mid-Atlantic seaboard states (think of having a "blast" in Chicago or gunshot "blasts" in Arkansas). M:F ratio is 10:1! Progression can be indolent to severe. No reliable skin test is available. Chest x-ray shows infiltrates that appear mass-like. Sputum shows large, single, broad-based budding yeasts (Image 13-13). Blastomycosis is more pyogenic than the others—patients can have purulent sputum. In children, it likes to disseminate to bone and skin.

Treatment of blastomycosis:

- Indolent: Observe or oral itraconazole.
- Severe: Amphotericin B. HIV patients require chronic suppression with itraconazole.

Allergic Bronchopulmonary Aspergillosis

Allergic bronchopulmonary aspergillosis (ABPA) is caused by an allergic reaction to *Aspergillus* in which there is immune complex deposition. There is usually a very high serum IgE. This allergy causes Type I (immediate wheal and flare; IgE-mediated) and Type III (5 hours), but not Type IV (delayed) reactions. Suspect it in asthmatics with worsening asthma symptoms, coughing up brownish mucous plugs (!), recurrent infiltrates, and peripheral eosinophilia. ABPA may occur in CF patients.

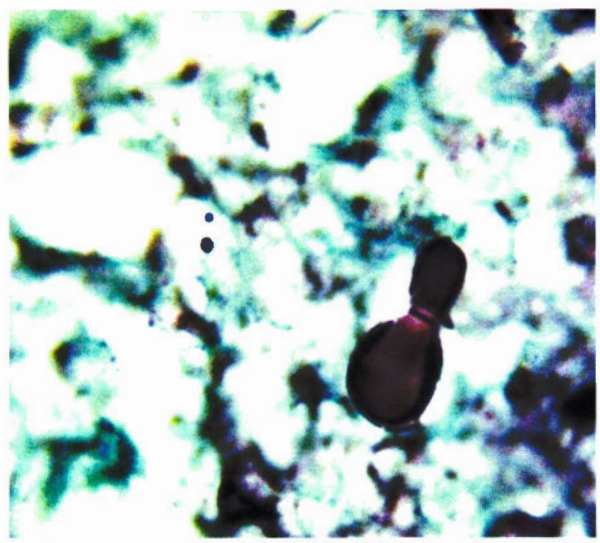
Chest x-ray and CT show central mucus impaction and central bronchiectasis causing a "fingers in glove"–appearing central infiltrate. Sputum may show branching hyphae (nonspecific). If there is only lung eosinophilia (no peripheral eos), consider instead a chronic eosinophilic pneumonia.

Treat ABPA with long-term corticosteroids and itraconazole.

ATYPICAL PNEUMONIAS

Overview

Atypical pneumonias usually occur in children older than 5 years of age. Patients typically have no sputum production, a nontoxic appearance, and a normal or slightly elevated WBC count. Atypical pneumonia may follow an upper respiratory infection. Atypical pneumonias can be caused by *Mycoplasma*, *Chlamydia pneumoniae* (TWAR), *Chlamydia psittaci* (bird farmers), *Legionella*, *Histoplasma*, *Coccidioides*, and viruses. Other causes include Q fever and tularemia. Consider tularemia in



Courtesy of CDC / Dora Ajello, MD

Image 13-13: Histopathology of Blastomycosis Budding Yeasts

Quick Quiz

- If you see the words "San Joaquin valley" on a test question, you need to look for which fungus on the exam?
- Name the geographical areas for coccidioidomycosis, blastomycosis, and histoplasmosis.
- An asthmatic presents with worsening wheezing and an extremely high IgE level. What do you suspect as an etiology?
- How do you treat ABPA?
- What are the extrapulmonary manifestations of *Mycoplasma* infection?
- Does having an abnormal sinus x-ray indicate bacterial infection in a child with asthma?

patients who hunt or skin animals and are from Arkansas or Missouri. Think of Q fever if the patient lives around cattle or sheep—these animals are naturally infected; the causative organism, *Coxiella burnetii*, is not transmitted between humans.

Mycoplasma pneumoniae

Mycoplasma pneumoniae is a common cause of community-acquired pneumonias in children older than 5 years of age and in adolescents. Having a 2–3-week incubation period, it spreads slowly (person-to-person). A prodrome of headache, fever, and pharyngitis is classic. It usually has an insidious onset, with the chest x-ray often appearing worse than the symptoms suggest. Occasionally, it has a more acute onset and can mimic a pneumococcal pneumonia.

Extrapulmonary manifestations of *Mycoplasma* pneumonia include hemolytic anemia, splenomegaly, erythema multiforme (and Stevens-Johnson syndrome), arthritis, myringitis bullosa, pharyngitis, tonsillitis, and neurologic changes—especially confusion. Diagnosis: Definitive is with an IgM antibody (think IgMMMycoplasma) and suggestive is with a positive cold agglutinin titer.

Treat with a macrolide or doxycycline. Patients sometimes take a long time (> 6 months) to fully recover!

Chlamydophila pneumoniae (formerly *Chlamydia*)

Chlamydophila pneumoniae is the TWAR pathogen. It causes epidemic pneumonia in older children and adolescents. It may be the cause of up to 10% of community-acquired pneumonias. Symptoms are similar to *Mycoplasma* pneumonia. Often there is a biphasic illness: The patient presents with a sore throat negative for group A strep, and, 2–3 weeks later, pneumonia develops. Treat with tetracycline/doxycycline or a macrolide.

ASTHMA

Asthma is the most common chronic disease of childhood. Prevalence data have shown increasing rates of asthma since the 1980s. Asthma is more common in African-Americans of all ages and in boys of all races. Asthma is quite variable in its presentation and course. Airway obstruction is the most common pathologic problem, which may be due to bronchial smooth muscle spasm, airway mucosa edema, mucus impaction of bronchi, airway inflammation, and/or airway hyperresponsiveness.

Diagnosis begins with the history and physical examination. Common symptoms include recurrent wheezing, shortness of breath, chest tightness, exercise intolerance, mucoid vomiting, and chronic cough. Various factors seem to trigger an asthma attack, including viruses, smoke, exercise, allergen exposure, breathing cold dry air, aspirin, aspiration, and acid reflux. Physical examination during "normal" times may not show anything or may show only a prolonged expiratory phase; during attacks, wheezing, chest hyperinflation, tachypnea, and use of accessory muscles can be present.

Children who wheeze during infancy continue to wheeze after the age of 6 years 15% of the time. Also, about 15% of children develop their first "wheezing" episode of asthma after the age of 6 years.

CLASSIFICATION OF ASTHMA

See Figure 13-1 to Figure 13-9 at the end of this section. Know this stepwise approach to asthma (updated late 2007) as issued by the National Asthma Education and Prevention Program (NAEPP) Coordinating Committee, coordinated by the National Heart, Lung, and Blood Institute (NHLBI) of the National Institutes of Health. Symptoms define whether the asthma is intermittent or persistent, and they also define the severity. Based on this classification, treatment regimens can be determined.

CONFOUNDING ISSUES IN ASTHMA

Sinusitis

It is known that children with asthma have a high incidence of abnormal sinus x-rays. However, we now know that a majority of these children likely do not have clinical bacterial sinusitis but rather simple acute nasopharyngitis with an abnormal sinus x-ray. Therefore, having an abnormal sinus x-ray and asthma does not equate to needing antibiotic therapy. Clinical diagnosis of sinusitis should be pursued before initiating antibiotic therapy.

GE Reflux

Gastroesophageal (GE) reflux can be a significant problem in the child with asthma. First, in the neonate, significant GE reflux may imitate asthma and lead to an incorrect diagnosis. Second, in older children, significant GE reflux can exacerbate underlying asthma and initiate an acute attack. Theophylline, which is used in some asthma therapy, can reduce the lower esophageal sphincter (LES) tone, resulting in increased risk of GE reflux.

Exercise

Exercise causes bronchodilatation and an increase in expiratory flow rates in normal as well as asthmatic children. Exercise-induced asthma is seen most commonly in adolescents who have no other signs or symptoms of asthma. They develop cough or difficulty breathing after 6–10 minutes of exercise, especially in cold, dry air. Pretreatment with cromolyn sodium (requires days or even weeks to work) or a short-acting β-adrenergic agent (right before exercise) may prevent or reduce the severity of symptoms.

The Difficult, Refractory Patient

Three things should come to mind if you are presented a patient who does not respond to routine therapies for asthma:

1) Wrong diagnosis: Consider CF, allergic bronchopulmonary aspergillosis, vocal cord dysfunction, hypersensitivity pneumonia, and sleep apnea.
2) Exacerbating factors; e.g., tobacco smoke exposure, GE reflux, and sinusitis.
3) Poor adherence to the treatment plan.

Note: ~ 5% of children will not respond to standard therapy and will require prolonged courses of corticosteroids to maintain a symptom-free period.

TREATMENT

Overview

The National Heart, Lung, and Blood Institute has published a comprehensive guideline for asthma management, which was updated in late 2007. The complete compendium is available online at: http://www.nhlbi.nih.gov/guidelines/asthma/asthgdln.htm

We've included the important figures from the guideline here in Figure 13-1 through Figure 13-9 at the end of this section. Be sure you know these! They vary by age and are based on the symptoms the patient is having.

For example, let's review a few key highlights. Note that for intermittent asthma, no daily medication is recommended for any age group. For mild persistent asthma (symptoms occurring > twice weekly but not daily), use low-dose inhaled corticosteroid as the preferred initial treatment for all age groups. If this agent does not control symptoms in a child ≤ 4 years of age, use a medium-dose inhaled corticosteroid. For children 5–11 years old who do not have symptoms controlled with a low-dose inhaled corticosteroid, use either a medium-dose inhaled corticosteroid or a low-dose inhaled corticosteroid combined with an inhaled long-acting β_2-agonist, or a leukotriene receptor antagonist, or theophylline. For a child ≥ 12 who is not controlled with a low-dose inhaled corticosteroid, use a low-dose inhaled corticosteroid plus a long-acting inhaled β_2-agonist or a medium-dose inhaled corticosteroid.

Know that in all patients who have an exacerbation, quick relief includes using a short-acting inhaled β_2-agonist (peak effect in 15 minutes, with duration of 4 hours); oral or parenteral corticosteroids also are recommended, depending on response. See Figure 13-9 for management of asthma exacerbations in the hospital or emergency department setting. Home and outpatient peak flow monitoring is an excellent method to monitor response to therapy and quality of control. Ensure that every child has a personal peak flow monitor and is educated about its use; then observe the child using the product. Education is the key to preventing exacerbations as well as to getting exacerbations under control quickly.

The goal is to get and keep the asthma under control: minimal or no daily (including nighttime) symptoms, minimal or no exacerbations, no limitations on daily activities, no missed school or work, minimal use of short-acting β_2-agonists, and minimal-to-no adverse effects from therapy. If these goals are met, reassess in 3 months and determine if you can "step down" to a less intense treatment regimen. If the symptoms are not being controlled, "step up" to a higher level of management and determine if the asthma can be better controlled.

Drug dosages are listed, but for the Board examination, you won't have to memorize specific dosages for most of the agents; in particular, you won't be responsible for remembering the "comparative" daily dosages for inhaled steroids.

Corticosteroids

Corticosteroids are the most effective antiinflammatory agents available for the treatment of asthma. They are formulated in oral, inhaled, and intravenous forms. Long-term use of systemic (oral, IV) corticosteroids has many adverse effects. You should especially know the following such effects from systemic steroids:

- Suppression of the hypothalamic-pituitary-adrenal axis
- Osteoporosis
- Cataracts
- Hyperglycemia
- Weight gain
- Thinning of the skin

Quick Quiz

- What is an effective preventative (or slightly preferred "preventative") therapy for exercise-induced asthma?
- Know the "step up" and the "step down" for management of asthmatics as they worsen or improve over time.
- Know that the AAP (and therefore likely the ABP) wants every child to have an objective home method to evaluate their asthma.
- What are some long-term complications of prolonged use of systemic steroids?
- What are some long-term complications of prolonged use of inhaled steroids?
- Should formoterol be used for rescue therapy in acute asthma attacks?
- What does adding erythromycin to a patient's regimen that already includes theophylline potentially do to the theophylline level?
- True or false? Nearly all cases of foreign body aspiration are diagnosed in the first few hours after aspiration.

- Striae
- Growth retardation

You must closely monitor patients on chronic oral steroids, especially for the first sign of infection or significant stressor, since those patients will not be able to mount an appropriate adrenal response due to suppression of the axis. There are multiple strengths and dosages. Most start with low doses and increase to higher doses to control symptoms as needed.

Use of inhaled steroids may potentially cause some of these particular problems:

- Growth velocity changes.
- Dermal thinning and increased ease of skin bruising.
- Rarely cataracts may form and hypothalamic-pituitary-adrenal axis function may be affected.
- Oral candidiasis (thrush) is common and can be prevented by using a spacer and rinsing the mouth after inhalation.

Cromolyn Sodium and Nedocromil Sodium

Cromolyn sodium is an antiinflammatory medication that may stabilize mast cell membranes, but its mechanism of action is not well understood. It is used in a multi-dose inhaler (MDI) form and for nebulization. It has a very good safety profile, with only occasional side effects of cough, dermatitis, myositis, and gastroenteritis. Nedocromil sodium may be more efficacious than cromolyn sodium.

Salmeterol and Formoterol (Long-acting Inhaled β_2-agonists)

These 2 agents provide bronchodilatation for up to 12 hours. The caveat for these agents is that they should not be used to treat an acute exacerbation; their onset of action is much slower than albuterol. Nor should they be used as monotherapy.

Leukotriene Modifiers

The available leukotriene modifiers are montelukast and zafirlukast. They are biologically active fatty acids derived from the oxidative metabolism of arachidonic acid. They work by inhibiting leukotriene binding to receptors. Montelukast has efficacy in preventing exercise-induced asthma. Side effects are rare.

Theophylline

Theophylline is a methylxanthine and requires serum monitoring of levels (serum concentrations of 5–15 mcg/mL are considered optimal). It has a slow onset of action as well and is not usually recommended for acute therapy. Toxicity will usually present with GI symptoms and behavioral effects. Drug-drug interactions are a particular problem: Oral contraceptives, erythromycin, ciprofloxacin, and cimetidine can cause toxic theophylline levels, while phenobarbital and phenytoin can decrease theophylline levels.

NON-ASTHMA CAUSES OF WHEEZING

ASPIRATION OF FOREIGN BODIES

Children place numerous objects in their mouths day in and day out and—luckily—aspiration is infrequent. The most commonly aspirated objects are seeds, nuts, and peanuts. Other common items include coins, hot dogs, small toys, balloons, jewelry, batteries, and firm vegetables. Materials most commonly lodge in the right main or left main bronchi, but objects can pretty much go anywhere. The child may acutely present with choking or coughing followed by wheezing, dyspnea, or stridor. However, you may have delay of the diagnosis for more than a month in as many as 20% of cases.

CXR can be very helpful even though most of these items are radiolucent. You will see obstructive asymmetric hyperinflation in nearly 66% of children who have bronchial foreign bodies; however, it should be noted that 10–25% will have a normal x-ray.

For children who are in distress and cannot get the foreign body up, consider any of a variety of techniques.

For infants younger than 1 year of age, most recommend turning the infant over (face down) and forcefully giving 5 back blows. For children older than 1 year of age, the Heimlich maneuver (subdiaphragmatic abdominal thrusts) should be the first intervention. Never do a blind finger sweep. This could cause the object to go further back (as well as put you at risk for the "bite that crazy doctor's finger off" scenario in the uncooperative child).

If the initial maneuvers are unsuccessful, a "jaw thrust" should be done. If the foreign body can be visualized, attempt to remove it with a Magill or other large forceps. If these methods fail and the child is unconscious or nonbreathing, establish a surgical airway distal to the obstruction.

Finally, if all the previous maneuvers fail, endoscopy should be performed by an experienced endoscopist to remove the foreign body. Antibiotics are not usually required.

BRONCHIOLITIS OBLITERANS / BOOP

Bronchiolitis Obliterans

Bronchiolitis obliterans can be caused by a variety of disorders, but in children, it most commonly occurs following a lower respiratory tract infection, particularly with adenovirus types 3, 7, or 21. Bronchiolitis obliterans occurs when small bronchi and bronchioles are obstructed by intraluminal masses of fibrous tissue that results in a chronic lung disease. Children can become infected *in utero* or throughout childhood, but the highest incidence occurs between 6 months and 2 years of age. Children who have adenovirus pneumonitis have nearly a 33% risk of developing chronic lung disease; this increases to nearly 66% in some Native American populations! Recently, the incidence has increased due to lung transplantation and also due to graft-versus-host disease associated with bone marrow transplant.

Bronchiolitis obliterans results in hypoxemia and hypercarbia because of poor gas exchange. Pulmonary edema becomes common over time. You must perform a lung biopsy to confirm diagnosis.

Treatment is supportive, with oxygen and avoidance of another lung injury. Treat pulmonary edema with diuretics. Corticosteroids have been advocated by some, based on adult data showing improvement.

Prognosis varies because some children improve by 8–10 years of age, while others develop debilitating chronic lung disease with the potential for respiratory failure and death.

Cryptogenic Organizing Pneumonia (COP)

COP occurs mostly in adults, although some children are affected. The etiologies include pneumonia, toxic inhalants, and collagen vascular diseases. With COP, which is distinct pathologically from bronchiolitis obliterans, the alveolar septa are thickened by a chronic inflammatory cell infiltrate, as well as the alveolar septa having Type II cell hyperplasia. Patients frequently will present with numerous episodes of "bronchitis" that respond to antibiotics and then recur. There are usually multiple cycles of bronchitis followed by antibiotics before you make a diagnosis. Corticosteroids are beneficial.

BRONCHIECTASIS

Bronchiectasis refers to "dilatation of the bronchi." The bronchi become damaged during an infection or inflammation and become distorted. It is usually irreversible.

Bronchiectasis can be focal or generalized. Children present with a chronic productive cough and wheezing, and have recurrent infections. Clubbing of the fingers is very common (Image 13-14). Affected children have a large total lung capacity, large functional residual capacity, and a small vital capacity. Areas of ventilation-perfusion mismatch are common. Etiologies of bronchiectasis include CF, chronic aspiration, dysmotile cilia syndromes, immune deficiencies, and allergic bronchopulmonary aspergillosis.

Image 13-14: Clubbing

Treatment includes bronchodilators with postural drainage. Antibiotic therapy may be required on an ongoing basis to prevent recurrent infections.

DYSMOTILE CILIA SYNDROMES

Overview

There are several rare disorders of cilia morphology that result in abnormal ciliary function. Normally, cilia beat synchronously at 7–22 times per second. Any impairment with the beat or the synchrony can result in poor mucociliary clearance and subsequent recurrent episodes of upper and lower respiratory tract infections. Kartagener syndrome (see below) is the most widely known disorder but is still quite rare. Treatment of these syndromes is the same as for bronchiectasis, and prognosis is good for those with cilia-related symptoms, with most having a normal lifespan.

Kartagener Syndrome

Kartagener syndrome occurs when one or both dynein arms of the cilia are absent. It presents with sinusitis, bronchiectasis, situs inversus, and reduced male fertility. It can be sporadic or familial in character and is autosomal recessive.

QuickQuiz

- Are antibiotics indicated in most cases of peanut aspiration?
- Which viruses most commonly cause bronchiolitis obliterans?
- How do you diagnose bronchiolitis obliterans?
- An adolescent presents with multiple episodes of "bronchitis" that clear with antibiotics and then recur in a month or two. He has had 6 episodes now. What diagnosis should you entertain?
- What is Kartagener syndrome?
- Compare and contrast apnea with periodic breathing.
- Is apnea of prematurity a risk factor for SIDS? Is prematurity itself a risk factor for SIDS?
- What "maneuver" has had the greatest impact on SIDS incidence?
- Does maternal smoking increase the risk of SIDS?

APNEA

Apnea is a common problem in premature infants, especially those < 32-weeks gestation. Apnea that occurs in a term infant requires extensive evaluation and scrutiny.

Apnea is defined as the absence of respiratory airflow and can be subdivided into:

1) Central: No respiratory effort, no airflow.
2) Obstructive: Respiratory effort is present with a paradoxic inward movement of the chest and outward movement of the abdomen and no airflow.
3) Mixed: Having both central and obstructive components.

It is abnormal for airflow to cease ≥ 20 seconds or to exhibit shorter episodes that are associated with bradycardia or cyanosis. The above must be contrasted with periodic breathing, which occurs when 3 or more respiratory pauses of ≥ 3 seconds occur with less than 20 seconds of respiration between pauses. Periodic breathing is considered normal in premature infants.

"Apnea of prematurity" is periodic breathing with apnea that occurs in a preterm infant; it usually resolves by 37-weeks gestation, although it can persist past term. If cyanosis or bradycardia occurs in apnea of prematurity, monitor and prescribe supplemental oxygen.

The most frequent causes of apnea are sleep-associated hypoxemia and GE reflux. Other causes can include infectious, CNS, metabolic, cardiac, drug, environmental, and anatomic etiologies.

Management depends on the etiology. Monitor heart rate, chest wall motion, and/or oxygen saturation. Other methods include tactile stimulation, oxygen, methylxanthines, nasal CPAP, and—in severe cases—nasal ventilation or intubation with mechanical ventilation. Methylxanthines, such as theophylline or caffeine, are used to stimulate respiratory drive but have side effects of jitteriness, tachycardia, GI distress, and feeding intolerance. Make sure that all caregivers know basic CPR.

Note: Neither apnea of infancy nor apnea of prematurity is a risk factor for SIDS, but prematurity itself is a risk factor for SIDS.

SUDDEN INFANT DEATH SYNDROME (SIDS)

SIDS is defined as the sudden death of an infant under the age of 1 year that remains unexplained after an intensive review, including a thorough autopsy, examination of the death scene, and review of the clinical history. In the U.S., SIDS is the 3rd leading cause of death in infants (1st is congenital anomalies and 2nd is prematurity-associated conditions). The SIDS death rate has decreased markedly since implementation of the "back to sleep" program emphasized placing infants on their backs to sleep. SIDS is a diagnosis of exclusion, and no specific etiology has been determined.

SIDS peaks between 2 and 4 months of age; it is rare in the first month of life, and almost all cases occur in the first 6 months of life. Boys are more commonly affected than girls. A higher incidence is associated with prematurity, intrauterine growth restriction (IUGR), winter months, the hours between midnight and 8 a.m., and Native American or African-American ethnicity. Recent evidence suggests that deaths can also occur while the infant is awake. Other factors associated with higher risk include low socioeconomic status, young maternal age, high parity, short interval between pregnancies, absent or late prenatal care, maternal UTI or STD, intrauterine cocaine or opiate exposure, smoking during pregnancy, and passive smoke exposure after delivery. There appears to be a slightly higher risk of SIDS in future siblings of SIDS infants. Breastfed infants have a lower risk, as do children who have received their immunizations. However, the underlying marked decrease in SIDS in the U.S. and worldwide is due to the practice of placing the infants on their backs to sleep.

DROWNING AND SUBMERSION EVENTS

Drowning is the 2nd major cause of unintentional death in children in the U.S. and is the leading cause of death in children < 5 years of age in California, Florida, and Arizona. 2 peaks of submersion injury occur: < 5 years of age (related to bathtubs and unsupervised swimming

pools) and 15–25-year-old males at lakes, beaches, and streams.

Hypoxia results in hypoxemia leading to tissue hypoxia and end-organ damage. Aspiration of fluid causes loss of surfactant and can produce pulmonary edema and acute respiratory distress syndrome (ARDS) with a normal CXR initially. Sequelae depend on the degree of organ dysfunction, including neurologic, cardiovascular, metabolic, and renal.

CPR should be done with the knowledge that cervical spinal cord injury may be present. Pulses are commonly weak and difficult to find in a hypothermic patient who presents with sinus bradycardia or atrial fibrillation—in general, chest compressions can be delayed for up to a minute to be sure a pulse is not present. Rescue breathing should be implemented as soon as possible. Postural drainage has no role. If breathing, give oxygen; if not breathing, intubate. Rewarm all hypothermic patients with a core temperature of < 33° C (92° F). Remove wet clothing. Because hypothermia is neuroprotective, all efforts of resuscitation should be continued until the temperature is 32–35° C (90–95° F); this may take up to several hours!

Some risk factors for poor prognosis include:

- Submersion > 10 minutes
- > 10 minutes elapsed before life support is begun at the scene
- Resuscitation takes > 25 minutes
- Age < 3 years
- Water temperature > 10° C (50° F)

However, there are no good early predictors of poor outcomes that can help determine when to discontinue resuscitation—normal neurologic recovery has occurred following prolonged submersion and hypoxia, especially in cold water. In contrast, one series showed that if there were no spontaneous, purposeful movements at 24 hours, then the outcomes were very poor with severe neurologic damage or death.

BRONCHOPULMONARY DYSPLASIA (BPD)

OVERVIEW

Bronchopulmonary dysplasia (BPD) generally develops in infants under the age of 30-weeks gestation and presents as persistent respiratory signs/symptoms related to respiratory failure at birth. The original definition was proposed in 1967 when most infants affected weighed > 1,500 grams. Today, it is very rare for BPD to occur in infants weighing this much. Most recognize a BPD patient as an infant with oxygen dependency, persistent signs of respiratory distress, and an abnormal CXR. The controversy is when to set the cutoff date: The original definition used 28 days of life for finding these abnormalities; currently, many use 36-weeks post-conceptional age as the defining age for BPD.

BPD causes increased airway resistance and reduced lung compliance. Infants present with wheezing, rales, tachypnea, hypoxemia, and increased work of breathing. Infants with BPD usually grow poorly and have increased caloric requirements.

Preventing BPD centers on 2 interventions:

1) Delaying premature birth past 30-weeks gestation
2) Using prenatal corticosteroid therapy to advance fetal lung development

Using parenteral vitamin A postnatally has been shown to reduce the incidence of BPD. Surfactant improves survival of premature infants but does not prevent BPD, and actually some data show surfactant may increase the incidence of BPD. Nitric oxide studies are currently underway.

RISK FACTORS FOR BPD

Risk factors for BPD have changed in the last 30 years. When it was defined, the main risk factors were premature birth and history of severe neonatal respiratory failure. Today, we know that a majority of children who develop signs and symptoms of BPD have only mild or delayed-onset respiratory failure. Why is this? It is likely that postnatal factors play a more important role—including infection, immunity, patent ductus, malnutrition, lung fluid balance, and micronutrient deficiencies. Also, we know that some centers have a much lower incidence of BPD than others, so environmental factors must play a role—including infection control, nursing care, and fluid management.

What causes BPD? The latest theories are that BPD occurs due to arrested acinar development, with abnormal growth of the alveolar capillaries. Thus, oxygen cannot reach the blood stream easily, resulting in chronic hypoxemia and the need for persistent supplemental oxygen.

TREATMENT OF BPD

Treatment is multi-disciplined and requires close follow-up. Low-flow oxygen is the cornerstone of therapy, with pulse oximetry geared toward 92–96%. Low flow prevents oxygen toxicity or respiratory depression. You can usually taper off oxygen therapy by 8–10 months of age. If oxygen therapy is effective, the infant should have weight gains of 20–40 grams per day. If weight gain does not occur, check to be sure oxygen therapy is adequate; if oxygen therapy is adequate, increase caloric intake.

Furosemide is very effective in improving lung mechanics and gas exchange, and it is usually added for children with a primary respiratory acidosis with renal compensation. Thiazides have not been shown to improve lung function.

QuickQuiz

- What 2 interventions may prevent BPD from developing?
- What is the cornerstone of therapy for BPD?
- Which diuretic is effective in improving BPD symptoms?
- Are corticosteroids recommended for BPD therapy?
- What gene is responsible for CF?
- What is the mode of inheritance for CF?
- Which factor correlates best with survival in CF patients?
- What sinus and nasal findings commonly occur in CF patients?
- Early in CF, which bacterial organisms are most likely to cause infection? What about later in CF?

Bronchodilator therapy is helpful in some and harmful in others, the latter especially in those with tracheomalacia. Corticosteroid therapy is not recommended for the treatment of BPD, and recent clinical trials showed no benefit in getting infants off the ventilator more quickly.

Infants with BPD are at increased risk of having serious complications from RSV infection. Use of an anti-RSV monoclonal antibody (palivizumab) or an RSV-IVIG has been shown to reduce the incidence of hospitalization. Most prefer the monoclonal antibody. You also must defer MMR and varicella vaccines for 9 months after the last dose of RSV-IVIG.

CYSTIC FIBROSIS

OVERVIEW

Cystic fibrosis (CF) is an autosomal recessive disorder involving a mutation of CFTR (CF transmembrane receptor, or the "CF gene") on the long arm of chromosome 7. The CF gene spans 256 Kb. The most common mutation (*ΔF508*) in the CF gene is a 3-base pair deletion that leads to the loss of a single phenylalanine at position 508. The *ΔF508* mutation is present in nearly 80% of all CF cases, but homozygosity for this mutation is only about 50%. There are more than 1,000 other mutations now identified at the CF locus. The resulting mutations cause abnormal ion transport across epithelial surfaces, including impermeable chloride channels and overactive sodium pumps. This results in viscid secretions in affected tissues and organs and further leads to blockage of ducts and air passages. The tissues most affected are the lungs, pancreas, intestinal mucous glands, liver, reproductive tracts, and sweat glands.

Median survival has increased from 10.6 years in 1966 to nearly 37 years today. Exercise appears to be an important factor, and the patient's level of fitness, even more than pulmonary function, correlates with longer survival.

CLINICAL MANIFESTATIONS

Respiratory Tract

CF patients universally have pansinusitis, which can be a helpful clue in a young child with persistent disease. Nasal polyps can occur in about 25% of patients with CF, and the finding of nasal polyps in a child under the age of 12 should guide you toward CF as a possible diagnosis. Eventually, clubbing of the digits occurs in almost every patient.

The lower respiratory tract is normal at birth. However, over time—with recurrent airway inflammation, chronic viscid mucus production, and recurrent infection—the child develops obstructive pulmonary disease. Initially, you may diagnose the child as having recurrent cough and wheezing with recurrent bronchiolitis, asthma, or pneumonia. Eventually, hyperinflation and crackles occur with the development of chronic diffuse bronchiectasis. Finding decreased FEF_{25-75} can indicate early obstructive disease. The obstructive component can later be evidenced by finding decreased FEV_1, decreased peak expiratory flow, and increased residual volume. Use of exercise testing and pulmonary functions are very helpful in following progression of the disease in the older child and adolescent.

Most patients with CF have chronic pulmonary infections with acute exacerbations. Early in the disease, the bacteria most commonly responsible for exacerbations are *Staphylococcus aureus*, *Haemophilus influenzae*, and common gram-negative organisms such as *Klebsiella*. Later, *Pseudomonas aeruginosa* becomes the predominant organism. The *Pseudomonas* in CF is characterized as being a more "mucoid" strain. Today, new pathogens have emerged as important in progressive pulmonary disease; these include *Aspergillus fumigatus*, *Burkholderia cepacia* species, *Alcaligenes xylosoxidans*, and *Stenotrophomonas maltophilia*. MRSA also has now become an increasingly prominent pathogen; nationwide incidence has increased to nearly 20%. Interestingly, infection outside the respiratory tract is unusual.

The rate of progression of lung disease is variable for each child. Worse prognosis is conferred by second-hand cigarette smoke and recurrent viral infections. Pulmonary complications can include pneumothorax, hemoptysis, atelectasis, pulmonary hypertension, cor pulmonale, and respiratory failure (Image 13-15).

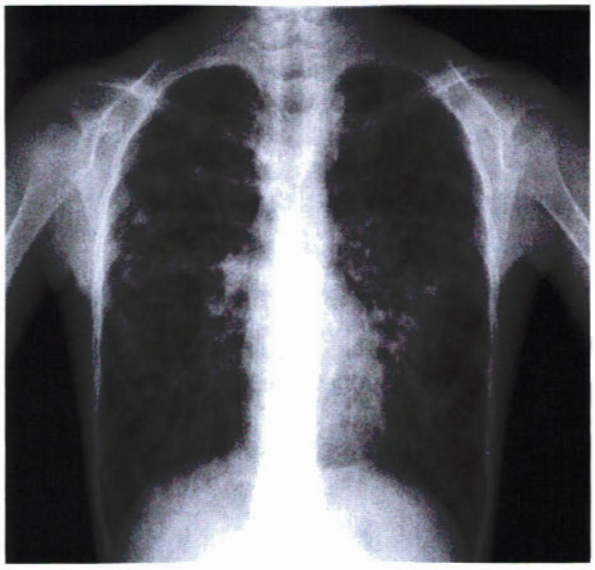


Image 13-15: Cystic Fibrosis Patient

GI Tract

Pancreatic insufficiency is present at birth in 50% of children with CF. Although 90% have signs/symptoms of pancreatic insufficiency by 9 years of age, diagnosis is delayed in about 10% with CF who do not have GI disease. Exocrine pancreatic insufficiency manifests with maldigestion of fats and proteins, which results in malabsorption, steatorrhea, and FTT.

Patients with CF who present at birth (about 10–20%) frequently do so with bowel obstruction, which is manifested by meconium ileus. In childhood, an additional 20–25% will have distal intestinal obstruction syndrome (DIOS, also known as meconium ileus equivalent). About 20% will have rectal prolapse during early childhood. Intussusception is much less common in CF than the above manifestations, but CF is one of the more common causes of intussusception in children older than 1 year of age. Other GI disorders found with increased frequency in CF patients are GE reflux, cholelithiasis, focal biliary cirrhosis, and nonspecific steatosis of the liver. Frank cirrhosis with liver failure is rare in CF, as is portal hypertension and its complications.

Sweat Glands

Sweat glands in CF patients produce a very high salt content, which has been a hallmark of the diagnosis. Sodium and chloride concentrations in CF patients' sweat are greater than 60 mEq/L (normal is < 40 mEq/L). Infants may develop severe hyponatremia. Because of these findings, the sweat test has been very helpful in diagnosing CF even today with molecular genetics.

Reproductive Tract

Males with CF have atresia of the vas deferens, which results in obstructive azoospermia and sterility. Males can have children by using *in vitro* methods. Females have thick cervical mucus, which also results in decreased fertility. Because of poor nutrition and/or chronic illness, many children with CF have delayed puberty.

Other Tissues

Knee and other joint pain can occur in CF due to hypertrophic pulmonary osteoarthropathy. It appears on x-ray as periosteal thickening of the long bones and adjacent joints.

A rare systemic vasculitis has been described in CF with arthritis and a skin rash.

DIAGNOSIS

Diagnosis is two-pronged.

First, at least one of the following is required:

- Typical features of CF (pulmonary disease, exocrine pancreas deficiency, sweat salt loss syndrome, male infertility)
- CF in a sibling
- Positive newborn screening test

and

Second, one of the following is required:

- Positive sweat test
- Identification of 2 CF mutations known to cause CF
- Abnormal nasal potential difference measurement

Because there are more than 1,000 mutations, it is still common for CF to be diagnosed with the sweat test. Sweat tests done in "CF centers" are reliable. Those done outside a reliable testing center have a high risk for false-positive and false-negative results! There are numerous reasons for false-positive results (> 60 mEq/L) but only 3 for false-negative (< 40 mEq/L): laboratory error (most common), edema due to hypoproteinemia, and rare CF mutations that do not result in sweat gland abnormalities. Who should have a sweat test? Obviously if FTT, steatorrhea, and chronic pulmonary disease are present, it is an easy decision. However, certain other findings should also make you suspicious; these are listed in Table 13-3. Many of these findings are "key word" clues that should get you looking for CF! Be suspicious: Why would a Board question mention "nasal polyps" in a physical examination or "male infertility" in a clinical history? The Boards like to give you clues. Make sure you look for them!

You can identify CF mutations by using blood, buccal brushings, or chorionic villous sampling. Most commercial labs look for 25 to 100 of the most common mutations, which can account for about 95% of all patients with CF. However, we know that 4% of the Caucasian population is heterozygous for the CF mutation, so finding one mutation does not rule in or rule out CF.

Quick Quiz

- When does pancreatic insufficiency occur in CF?
- What GI findings are more common in CF?
- What is the abnormality of the sweat glands in patients with CF?
- What is the abnormality of the reproductive tract in males with CF? Females?
- What is the joint finding in some patients with CF?
- What is the protocol for diagnosing CF?
- Who should get a sweat test?

The nasal potential difference test measures the bioelectric voltage difference across nasal epithelium and is done only in a few CF centers.

Newborn screening has become routine in many states, looking for an elevated blood immunoreactive trypsinogen (IRT). It has few false negatives but > 90% false positives. Depending on the State, if the IRT is abnormal it may be repeated or sent for mutation analysis. PCR testing for the most common mutations (*ΔF508* in particular) has also been used.

Table 13-3: Reasons to Consider Sweat Testing

GI Pearls for Testing:
Meconium ileus
Rectal prolapse
Prolonged neonatal jaundice
Chronic diarrhea
Steatorrhea
Respiratory Pearls for Testing:
Nasal polyps
Pansinusitis
Chronic cough
Recurrent wheezing
Staphylococcus aureus pneumonia
Finding *Pseudomonas* in throat, sputum, or bronchus cultures
Miscellaneous Pearls for Testing:
Digital clubbing
Family history of CF
FTT
"My baby tastes salty"
Male infertility

TREATMENT OF CF

Cystic Fibrosis Centers

Data have shown that survival is greatest for those children followed in CF centers.

Therapy for Pulmonary Disease

Chest physical therapy and postural drainage are the hallmarks of all treatment programs. Chest physical therapy is directed at all pulmonary segments at least 1–4 times daily routinely and is increased during exacerbations.

Exercise, particularly swimming and jogging, is beneficial.

Inhalational therapy can include bronchodilators, mucolytic agents (N-acetylcysteine), recombinant human DNase, and antibiotics (aminoglycosides and semisynthetic penicillins). Each of these may benefit the individual patient or may actually worsen the patient's symptoms; thus, each must be taken on a case-by-case basis. Newer treatments include amiloride, gene therapy, and uridine triphosphate (UTP), but these treatments are still undergoing clinical trials.

The use of prophylactic macrolide therapy (azithromycin once daily on M, W, F) as antiinflammatory therapy has been shown to decrease exacerbations, decrease hospitalizations, improve pulmonary function, and result in small increases in weight. Additionally, high-dose ibuprofen is being used by some centers because of its antiinflammatory effects.

Corticosteroids have been shown to be beneficial in some trials but have obvious side effects/drawbacks. Most likely, corticosteroids benefit those with asthma as well.

Antibiotics have probably provided the greatest benefit in prognosis. Treatment of exacerbations with anti-staphylococcal and anti-pseudomonal drugs is paramount. Once *Pseudomonas* is in the respiratory tree, it is almost impossible to rid the colonization. It is particularly bad if a mucoid form establishes itself. Quinolone use in CF is widespread, and data to date have not shown significant bony or cartilage abnormalities.

Use of antibiotics varies from center to center and patient to patient, but 3 general categories emerge:

1) Use of continuous inhaled or oral prophylactic antibiotics with addition of IV antibiotics for acute exacerbations
2) No antibiotics except with exacerbations
3) Aggressive antibiotics (oral, aerosol, or IV) based on sputum cultures, for 2–3 weeks every 1–2 months for patients with any evidence of pulmonary disease

In many centers, oral antibiotics are given at the first sign of pulmonary exacerbation. Aerosolized antibiotics, particularly tobramycin, can be useful as therapy to keep *Pseudomonas* colonization from causing an exacerbation or to treat in the midst of an acute

exacerbation. IV antibiotics are indicated when the patient either does not respond to outpatient therapy or else presents with a moderate-to-severe exacerbation. Antibiotic choices include the aminoglycosides (frequently tobramycin is used followed by gentamicin or amikacin), semisynthetic antipseudomonal penicillins (ticarcillin, ticarcillin-clavulanate, piperacillin-tazobactam), imipenem or meropenem, ceftazidime, aztreonam, quinolones, and (rarely) colistin. Note: Do not use ceftriaxone for *Pseudomonas*. Intravenous therapy is continued until the patient has clinically improved or reached a new plateau of functioning. This commonly takes 2–3 weeks but can take longer.

COMPLICATIONS

Pneumothorax

Pneumothorax (Image 13-16) occurs in about 10% of CF patients and can be a common cause of chest pain. Many resolve with bedrest and oxygen therapy, but some require chest tube placement, and a majority of patients have recurrence. Prevention of recurrences has been aided by the use of open thoracotomy through a small subaxillary incision, excision of apical blebs, stripping the apical pleura, and manual abrasion of the remaining accessible pleura. A caveat is that some transplant centers view surgical or chemical ablation of pleura as a contraindication for lung transplant.

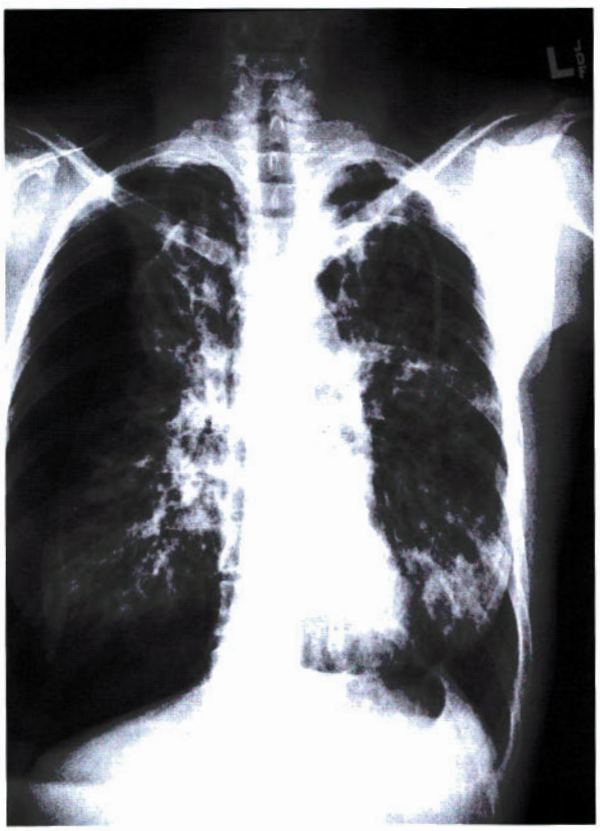


Image 13-16: Right Pneumothorax

Hemoptysis

Hemoptysis involving blood-streaked sputum is quite common. Hemoptysis of more than 300 mL in 24 hours occurs in only about 5–10% of patients and rarely is significant enough to require transfusions or other interventions. If hemoptysis occurs, it is usually due to infection, so IV antibiotics and aggressive chest physical therapy should be performed; chest physical therapy seems contradictory in a hemoptysis patient, but that is nonetheless the best therapy. Vitamin K deficiency should also be suspected in brisk bleeding because of the malabsorption of fat-soluble vitamins.

Pulmonary Hypertension

Pulmonary hypertension with the development of cor pulmonale and enlargement of the right ventricle is common in late CF. Heart failure with peripheral edema and hepatomegaly are poor prognostic signs and usually indicate survival of less than 8 months. Standard therapy of oxygen, salt restriction, and diuretics will be beneficial; do not use digitalis unless there is accompanying left ventricular dysfunction. Combined heart-lung transplant has been used in CF patients with cor pulmonale and severe lung disease.

Nutritional Abnormalities

Growth with normal weight-to-height ratio has been shown to be an important prognostic factor in keeping CF patients' lung function healthy. Thus, nutritional efforts are aggressive in helping these patients gain weight and encouraging them with sound nutritional guidance. Use of pancreatic enzyme replacement has become a cornerstone of therapy. Dosages of enzymes must be titrated to the individual patient. H_2 blockers may enhance the bioavailability of the enzymes.

Vitamin A and E supplements are necessary. Most patients with CF require 100–150% of the RDA for their age; for those patients who have difficulty gaining weight, a high-fat diet may be beneficial. Some patients cannot keep up with the daily intake required to gain weight and require nighttime enteral feeds to provide enough calories.

Abdominal complaints are common in patients with CF. Constipation is a recurrent complaint. Chronic constipation can lead to distal intestinal obstruction (DIOS), so institute active therapy to relieve constipation. Lactulose and polyethylene glycol 3350 (MiraLAX®, GlycoLax®) are used to prevent chronic constipation. If DIOS occurs, it can be treated with polyethylene glycol with added electrolytes (GoLYTELY®, CoLyte®) orally (if obstruction has not yet occurred) or hyperosmolar enemas such as meglumine diatrizoate. Rectal prolapse can be reversed with gentle manual pressure.

QuickQuiz

- Is ceftriaxone acceptable therapy for *Pseudomonas*?
- Is pneumothorax a concern in patients with CF?
- Which vitamin deficiency would you worry about in a CF patient who has prolonged episodes of hemoptysis or uncontrolled bleeding?
- What liver abnormality is seen in children with α_1-antitrypsin deficiency?

α_1-ANTITRYPSIN DEFICIENCY

α_1-antitrypsin deficiency rarely causes pulmonary symptoms in children, and it typically does not manifest until the 5th decade. The alleles responsible for α_1-antitrypsin deficiency occur on a locus called *Pi*. The most common allele is *Pi M*. The M means it moves moderately fast on an electrophoretic strip. There are variants of *Pi M*—some move faster (*Pi F*) and some slower (*Pi Z*). Only patients homozygous for the slower allele (Pi^{ZZ}) get severely decreased levels of α_1-antitrypsin. The normal level is 212 +/– 32 mg/dL. Heterozygotes (Pi^{MZ}) have > 80 mg/dL. Homozygotes (Pi^{ZZ}) have about 10–20 mg/dL.

Heterozygotes (defined by α_1-antitrypsin level > 80 mg/dL) have no increase in pulmonary disease unless they smoke. Know that about 15% of persons with the homozygote Pi^{ZZ} phenotype also get progressive liver fibrosis and cirrhosis—especially common in children. With this type of cirrhosis, as with cirrhosis of any cause, there is an increased incidence of hepatoma.

Suspect homozygous α_1-antitrypsin deficiency in nonsmokers with early-onset COPD—typically with the emphysematous bullae in the bases.

Treatment: Give α_1-antitrypsin by monthly IV infusions only for those with an α_1-antitrypsin level < 80 mg/dL and who exhibit mild-moderate obstructive pulmonary mechanics. These patients should be having pulmonary symptoms before starting treatment because, amazingly, some nonsmoking Pi^{ZZ} genotypes never get COPD. (100% of smokers with Pi^{ZZ} get emphysema at an early age!) Even though IV infusion of α_1-antitrypsin increases blood levels, as yet there is no data showing that α_1-antitrypsin infusion reverses or even stabilizes the lung disease process. When the emphysema is severe, the only treatment is lung transplantation.

HEMOPTYSIS

Hemoptysis is the presence of blood in the sputum or the spitting up of blood; it is rare in children ≤ 6 years because they generally swallow their sputum.

The most common etiologies in children are infection, foreign bodies, and bronchiectasis. Rarer causes include vasculitides (HSP, Wegener's, Goodpasture's, and SLE), congenital heart and lung defects, neoplasm, AV malformation, hemangioma, trauma, pulmonary embolism, and idiopathic (essential hemoptysis).

Evaluate by localizing the bleeding source if possible: Is it gastrointestinal in origin (look for coffee-ground appearance or food)? Or is it respiratory tract in origin (bright red or rust colored, "frothy," or mixed with sputum)?

Other signs/symptoms may be helpful in determining the etiology:

- Fever or chills: pneumonia, lung abscess
- Illicit drug use: cocaine smoking
- Hematuria: Wegener's or Goodpasture's
- Telangiectasia: A-V malformations
- Clubbing: chronic lung disease or congenital heart disease

Do a chest radiograph in the initial evaluation, but up to 33% of patients will have a normal CXR. Proceed to CT scan of the lung if the diagnosis is not clear. Bronchoscopy with bronchoalveolar lavage (BAL) is the next step after bleeding is controlled; the finding of hemosiderin-laden macrophages is diagnostic for pulmonary bleeding (they usually appear 3 days after bleeding). If the BAL is positive, then an echocardiogram is recommended. If the echocardiogram is normal, look for pulmonary-renal syndromes, bleeding abnormalities, or suspect idiopathic pulmonary hemosiderosis (next topic). Lung biopsy is done in most children with diffuse alveolar hemorrhage.

Management of most cases of hemoptysis is supportive because a majority of cases with mild hemoptysis resolve spontaneously and do not recur. For more extensive disease, follow the ABCs of life support. Hemostasis and embolotherapy are indicated for severe bleeding and require specialist intervention.

IDIOPATHIC PULMONARY HEMOSIDEROSIS (IPH)

Hemosiderosis is rare, but it appears in the content specifications of the ABP; so we will cover it here briefly. Recurrent pulmonary bleeding (alveolar hemorrhage in particular) may eventually cause pulmonary hemosiderosis. When no underlying etiology for repeated hemorrhages occurs, it is called idiopathic pulmonary hemosiderosis (IPH). Children usually present before the age of 10 years with either an abrupt hemoptysis or a progressive course of anemia, fatigue, and recurrent cough. Most patients present with iron deficiency anemia and frequently develop pulmonary fibrosis.

Sputum will show hemosiderin-laden macrophages without evidence of vasculitis or other diseases such as granulomatous lung disease or immunoglobin deposition disease. Corticosteroids are used in acute episodes, but the response varies. Children generally have a more rapid course and poorer prognosis than adults.

INTERSTITIAL LUNG DISEASES (ILDS)

SARCOIDOSIS

Sarcoidosis: "Noncaseating granuloma" is a multisystem disease that is rare in children. Chest x-ray findings are variable. Usually, there is bilateral hilar and/or mediastinal adenopathy +/– reticulonodular or alveolar infiltrates. Pulmonary function tests (PFTs) may either be normal or show restrictive +/– obstructive mechanics. The radiographic staging of sarcoidosis (Table 13-4) illustrates the interesting point that hilar adenopathy disappears as the disease progresses. 40–60% of children with sarcoidosis have hilar adenopathy alone or in combination with parenchymal infiltrates. Serum angiotensin-converting enzyme (SACE) level is nonspecific and considered of no use in diagnosis, but it may be useful for monitoring progression of disease (controversial). If the SACE level was previously elevated when the disease was active and low when inactive, it may be useful in determining if the disease is once again active. Hypercalcemia, hypercalciuria, and hypergammaglobulinemia are seen.

Sarcoidosis is a diagnosis of exclusion. A positive bronchoalveolar lavage shows an increased number of lymphocytes with a helper:suppressor ratio of > 4:1 (hypersensitivity pneumonitis has a ratio of < 1:1). It is imperative to exclude the other granulomatous diseases, including hypersensitivity pneumonitis, berylliosis, and infectious diseases caused by mycobacteria and fungi. Material for histological exam should be cultured as well as examined for organisms. While ensuring no organisms are present and cultures are negative, the best method for diagnosing sarcoidosis is by fiberoptic bronchoscopy with transbronchial or bronchial wall biopsies showing noncaseating granuloma.

Erythema nodosum is an associated skin lesion that denotes a good prognosis!

Table 13-4: Radiographic Staging of Sarcoidosis

Stage	Chest X-ray Findings
0	Clear
I	Bilateral hilar adenopathy
II	Adenopathy + parenchymal infiltrates
III	Diffuse parenchymal infiltrates
IV	Fibrosis, bullae, cavities

Treatment: Overall, 75% of sarcoid patients recover without treatment. It rarely progresses to pulmonary fibrosis or pulmonary hypertension. Severe disease is treated with corticosteroids for lack of anything better. There is no set regimen. Corticosteroids have not been proven to induce remissions in sarcoidosis, although they do decrease the symptoms and PFTs improve. Inhaled corticosteroids decrease the respiratory symptoms and may be used instead of systemic corticosteroids if the disease is primarily in the bronchi.

Indications for systemic corticosteroids:

- Eyes involvement
- Heart conduction abnormalities
- CNS involvement
- Severe pulmonary symptoms
- Severe skin lesions
- Persistent hypercalcemia

Other medications include methotrexate and thalidomide.

ALVEOLAR PROTEINOSIS

Alveolar proteinosis is usually more alveolar than interstitial. There are defective alveolar macrophages causing a buildup of pulmonary surfactant. Symptoms are similar to those in silicosis, but there is no history of exposure to silica. Often patients are hypoxemic from a large right-to-left shunt. Diagnosis is usually confirmed with open lung biopsy, but transbronchial biopsy or BAL is also okay. Treatment: If severe, do a whole lung lavage under general anesthesia. GM-CSF is a treatment that may restore proper function to the alveolar macrophages.

COLLAGEN-VASCULAR DISEASES ASSOCIATED WITH ILD

Systemic lupus erythematosus (SLE) causes painful pleuritis +/– effusion, but additionally it causes diffuse atelectasis and sometimes diaphragmatic weakness (and therefore, orthopneic dyspnea out of proportion to the chest x-ray findings, although the chest x-ray may show elevated diaphragms). SLE also occasionally causes hemoptysis similar to that in idiopathic pulmonary hemosiderosis (IPH). SLE affects both lung and pleura more frequently than any other collagen vascular disease (60%), while scleroderma affects the lung alone more than any other collagen vascular disease (100%! but no pleural changes). So, not much in the way of ILD with SLE!

Scleroderma has 2 lung effects:

1) Interstitial fibrosis (as just mentioned)
2) Intimal proliferation

It is this intimal proliferation in the pulmonary artery that causes pulmonary hypertension out of proportion to the pulmonary disease. So it is not the ILD but the intimal proliferation that causes the real pulmonary problem

QuickQuiz

- What does the CXR characteristically show in sarcoidosis?
- What does the biopsy of a hilar lymph node in sarcoidosis show?
- True or false? Scleroderma causes pulmonary hypertension out of proportion to the pulmonary disease noted.
- Which laboratory test is positive in many patients with Wegener granulomatosis?

in scleroderma patients. Scleroderma is often associated with pneumonia.

Sjögren's causes desiccation of the airways and is also associated with lymphocytic interstitial pneumonia (LIP).

VASCULITIDES THAT CAUSE ILD

Wegener Granulomatosis

Wegener granulomatosis—"necrotizing granuloma" (buzzword)—is a vasculitis that:

- Affects the upper respiratory tract and paranasal sinuses
- Causes a granulomatous pulmonary vasculitis with large (sometimes cavitary) nodules
- Causes a necrotizing glomerulonephritis

It sometimes is limited just to the lungs.

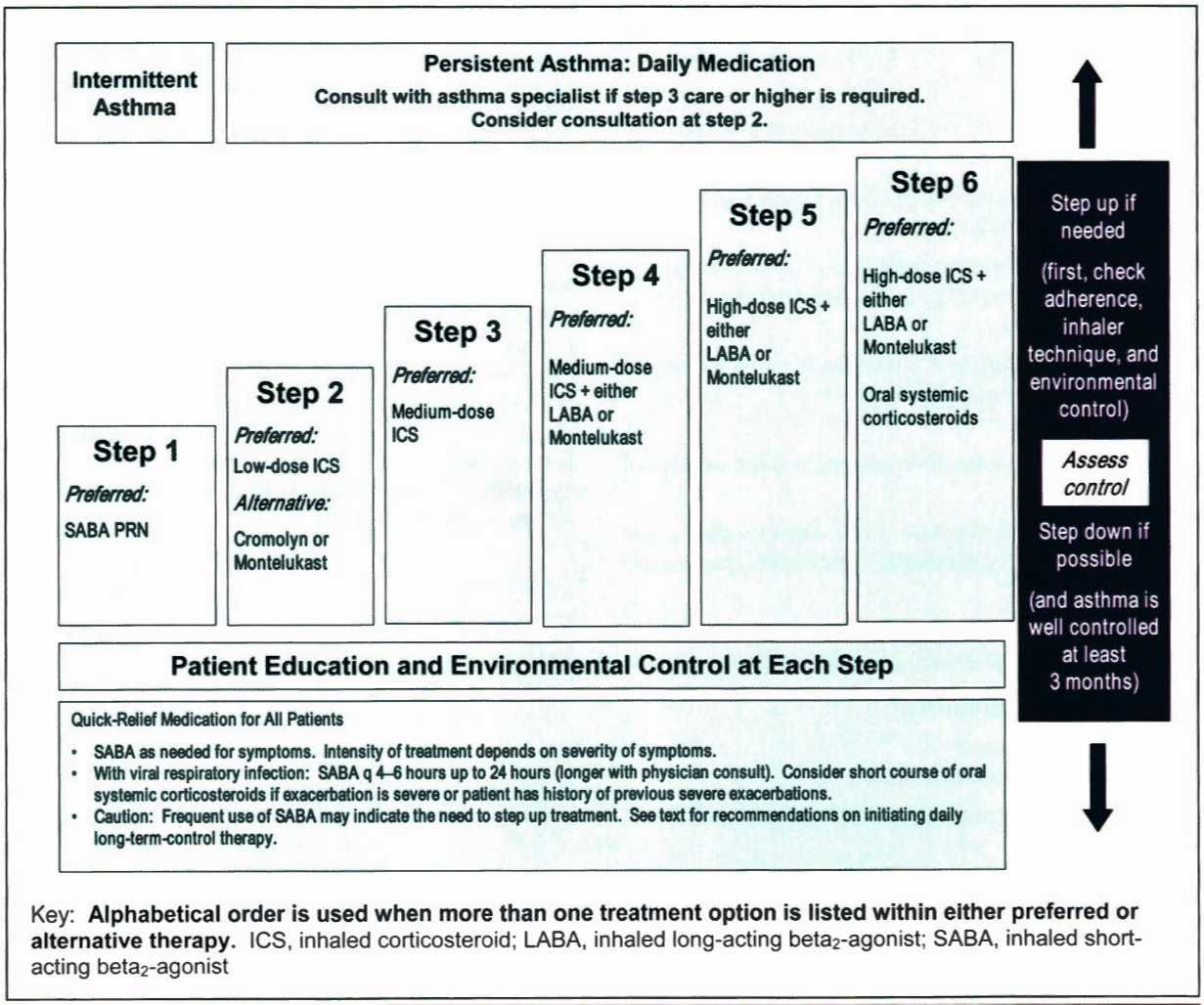
The ANCA test (antineutrophil cytoplasmic antibody—thought to be a destructive autoantibody) is often used as an adjunctive test. It is about 90% sensitive and 90% specific. When positive in a patient with Wegener granulomatosis, it is virtually always c-ANCA (96%); polyarteritis is usually p-ANCA positive.

You can confirm diagnosis from either a biopsy of the nasal membrane or an open lung biopsy. A kidney biopsy is not part of the diagnostic workup because it may not show the granulomas and is much more invasive. Treatment of Wegener granulomatosis: Cyclophosphamide with or without corticosteroids.

Remember: Kidney, lungs, and sinuses. Consider Wegener granulomatosis in any Board question that presents with a purulent nasal discharge, epistaxis, and/or signs of a glomerulonephritis with hematuria. The patient is not dyspneic and may or may not have a nonproductive cough or hemoptysis. If dyspneic and ANCA-negative, think Goodpasture syndrome.

Goodpasture Syndrome

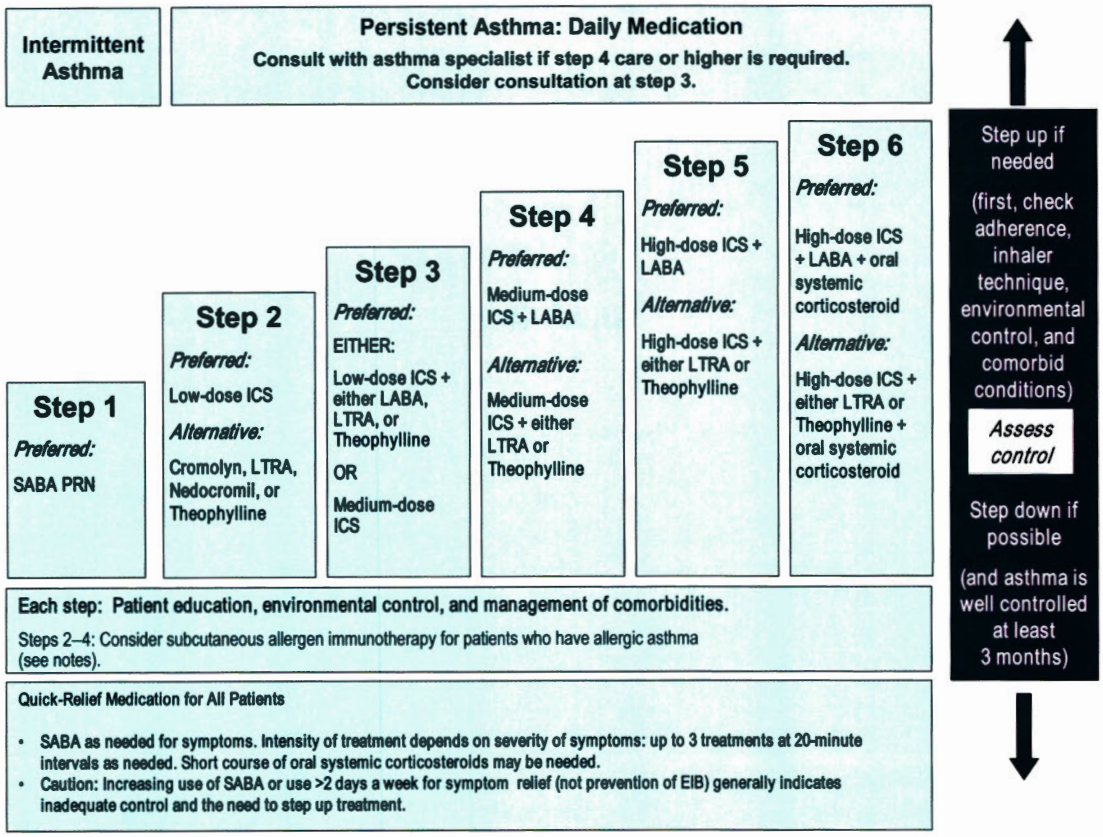
Goodpasture syndrome is of autoimmune etiology. It usually presents in young adult males with a male-to-female ratio of 3:1. Lung disease is the same as IPH (above), but Goodpasture syndrome also affects the kidneys. Usually, there is no frank hemorrhage, but often there is hemoptysis that precedes renal abnormalities. Like patients with IPH, patients with Goodpasture syndrome also may have Fe deficiency anemia. Symptoms are due to antiglomerular basement membrane antibodies, which result in linear deposition of IgG and C3 on alveolar and glomerular basement membranes. Treat with immunosuppressives and plasmapheresis. If the patient does have severe pulmonary hemorrhages, nephrectomy may help. Think of this disease if the patient presents with dyspnea, hemoptysis, Fe deficiency anemia, and glomerulonephritis but without upper airway signs (Wegener's).



Key: **Alphabetical order is used when more than one treatment option is listed within either preferred or alternative therapy.** ICS, inhaled corticosteroid; LABA, inhaled long-acting beta$_2$-agonist; SABA, inhaled short-acting beta$_2$-agonist

Figure 13-1: Stepwise Approach for Managing Asthma in Children 0–4 Years of Age

Source for Figures 13-1 through 13-9: Expert Panel Report 3: Guidelines for Diagnosis and Management of Asthma, by National Asthma Education and Prevention Program (NAEPP) Coordinating Committee/National Heart, Lung, and Blood Institute (NHLBI) of the National Institutes of Health (NIH) [Updated 2007]



Key: **Alphabetical order is used when more than one treatment option is listed within either preferred or alternative therapy.** ICS, inhaled corticosteroid; LABA, inhaled long-acting beta$_2$-agonist, LTRA, leukotriene receptor antagonist; SABA, inhaled short-acting beta$_2$-agonist

Figure 13-2: Stepwise Approach for Managing Asthma in Children 5–11 Years of Age

Assessing severity and initiating therapy in children who are not currently taking long-term control medication

Classification of Asthma Severity (0–4 years of age)

Components of Severity		Intermittent	Persistent: Mild	Persistent: Moderate	Persistent: Severe
Impairment	Symptoms	≤2 days/week	>2 days/week but not daily	Daily	Throughout the day
	Nighttime awakenings	0	1–2x/month	3–4x/month	>1x/week
	Short-acting $beta_2$-agonist use for symptom control (not prevention of EIB)	≤2 days/week	>2 days/week but not daily	Daily	Several times per day
	Interference with normal activity	None	Minor limitation	Some limitation	Extremely limited
Risk	Exacerbations requiring oral systemic corticosteroids	0–1/year	≥2 exacerbations in 6 months requiring oral systemic corticosteroids, or ≥4 wheezing episodes/1 year lasting >1 day AND risk factors for persistent asthma		
		← Consider severity and interval since last exacerbation. Frequency and severity may fluctuate over time. →			
		Exacerbations of any severity may occur in patients in any severity category.			
Recommended Step for Initiating Therapy		Step 1	Step 2	Step 3 and consider short course of oral systemic corticosteroids	

(See figure 4–1a for treatment steps.)

In 2–6 weeks, depending on severity, evaluate level of asthma control that is achieved. If no clear benefit is observed in 4–6 weeks, consider adjusting therapy or alternative diagnoses.

Key: EIB, exercise-induced bronchospasm

Figure 13-3: Classifying Asthma Severity and Initiating Treatment in Children 0–4 Years of Age

Note: Figure 4-1a referred to in this table (treatment steps) is the same as MedStudy Figure 13-1 on page 13-30.

Assessing severity and initiating therapy in children who are not currently taking long-term control medication

Components of Severity		Classification of Asthma Severity (5–11 years of age)			
			Persistent		
		Intermittent	Mild	Moderate	Severe
Impairment	Symptoms	≤2 days/week	>2 days/week but not daily	Daily	Throughout the day
	Nighttime awakenings	≤2x/month	3–4x/month	>1x/week but not nightly	Often 7x/week
	Short-acting $beta_2$-agonist use for symptom control (not prevention of EIB)	≤2 days/week	>2 days/week but not daily	Daily	Several times per day
	Interference with normal activity	None	Minor limitation	Some limitation	Extremely limited
	Lung function	• Normal FEV_1 between exacerbations • FEV_1 >80% predicted • FEV_1/FVC >85%	• FEV_1 = >80% predicted • FEV_1/FVC >80%	• FEV_1 = 60–80% predicted • FEV_1/FVC = 75–80%	• FEV_1 <60% predicted • FEV_1/FVC <75%
Risk	Exacerbations requiring oral systemic corticosteroids	0–1/year (see note)	≥2/year (see note) →		
		← Consider severity and interval since last exacerbation. Frequency and severity may fluctuate over time for patients in any severity category. →			
		Relative annual risk of exacerbations may be related to FEV_1.			
Recommended Step for Initiating Therapy (See figure 4–1b for treatment steps.)		Step 1	Step 2	Step 3, medium-dose ICS option and consider short course of oral systemic corticosteroids	Step 3, medium-dose ICS option, or step 4 and consider short course of oral systemic corticosteroids
		In 2–6 weeks, evaluate level of asthma control that is achieved, and adjust therapy accordingly.			

Key: EIB, exercise-induced bronchospasm; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; ICS, inhaled corticosteroids

Figure 13-4: Classifying Asthma Severity and Initiating Treatment in Children 5–11 Years of Age

Note: Figure 4-1b referred to in this table (treatment steps) is the same as MedStudy Figure 13-2 on page 13-31.

Classification of Asthma Control (0–4 years of age)

Components of Control		Well Controlled	Not Well Controlled	Very Poorly Controlled
Impairment	Symptoms	≤2 days/week	>2 days/week	Throughout the day
	Nighttime awakenings	≤1x/month	>1x/month	>1x/week
	Interference with normal activity	None	Some limitation	Extremely limited
	Short-acting $beta_2$-agonist use for symptom control (not prevention of EIB)	≤2 days/week	>2 days/week	Several times per day
Risk	Exacerbations requiring oral systemic corticosteroids	0–1/year	2–3/year	>3/year
	Treatment-related adverse effects	Medication side effects can vary in intensity from none to very troublesome and worrisome. The level of intensity does not correlate to specific levels of control but should be considered in the overall assessment of risk.		
Recommended Action for Treatment (See figure 4–1a for treatment steps.)		• Maintain current treatment. • Regular followup every 1–6 months. • Consider step down if well controlled for at least 3 months.	• Step up (1 step) and • Reevaluate in 2–6 weeks. • If no clear benefit in 4–6 weeks, consider alternative diagnoses or adjusting therapy. • For side effects, consider alternative treatment options.	• Consider short course of oral systemic corticosteroids, • Step up (1–2 steps), and • Reevaluate in 2 weeks. • If no clear benefit in 4–6 weeks, consider alternative diagnoses or adjusting therapy. • For side effects, consider alternative treatment options.

Key: EIB, exercise-induced bronchospasm

Figure 13-5: Assessing Asthma Control and Adjusting Therapy in Children 0–4 Years of Age

Note: Figure 4-1a referred to in this table (treatment steps) is the same as MedStudy Figure 13-1 on page 13-30.

Components of Control		Classification of Asthma Control (5–11 years of age)		
		Well Controlled	Not Well Controlled	Very Poorly Controlled
Impairment	Symptoms	≤2 days/week but not more than once on each day	>2 days/week or multiple times on ≤2 days/week	Throughout the day
	Nighttime awakenings	≤1x/month	≥2x/month	≥2x/week
	Interference with normal activity	None	Some limitation	Extremely limited
	Short-acting $beta_2$-agonist use for symptom control (not prevention of EIB)	≤2 days/week	>2 days/week	Several times per day
	Lung function			
	• FEV_1 or peak flow	>80% predicted/ personal best	60–80% predicted/ personal best	<60% predicted/ personal best
	• FEV_1/FVC	>80%	75–80%	<75%
	Exacerbations requiring oral systemic corticosteroids	0–1/year	≥2/year (see note)	
		Consider severity and interval since last exacerbation		
Risk	Reduction in lung growth	Evaluation requires long-term followup.		
	Treatment-related adverse effects	Medication side effects can vary in intensity from none to very troublesome and worrisome. The level of intensity does not correlate to specific levels of control but should be considered in the overall assessment of risk.		
Recommended Action for Treatment (See figure 4–1b for treatment steps.)		• Maintain current step. • Regular followup every 1–6 months. • Consider step down if well controlled for at least 3 months.	• Step up at least 1 step and • Reevaluate in 2–6 weeks. • For side effects: consider alternative treatment options.	• Consider short course of oral systemic corticosteroids, • Step up 1–2 steps, and • Reevaluate in 2 weeks. • For side effects, consider alternative treatment options.

Key: EIB, exercise-induced bronchospasm; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity

Figure 13-6: Assessing Asthma Control and Adjusting Therapy in Children 5–11 Years of Age

Note: Figure 4-1b referred to in this table (treatment steps) is the same as MedStudy Figure 13-2 on page 13-31.

Medication	Dosage Form	0–4 years	5–11 years	Comments
Systemic Corticosteroids				***(Applies to all three corticosteroids)***
Methylprednisolone	2, 4, 8, 16, 32 mg tablets	0.25–2 mg/kg daily in single dose in a.m. or qod as needed for control	0.25–2 mg/kg daily in single dose in a.m. or qod as needed for control	■ For long-term treatment of severe persistent asthma, administer single dose in a.m. either daily or on alternate days (alternate-day therapy may produce less adrenal suppression).
Prednisolone	5 mg tablets, 5 mg/5 cc, 15 mg/5 cc	Short-course "burst": 1–2 mg/kg/day, maximum 60 mg/day for 3–10 days	Short-course "burst": 1–2 mg/kg/day, maximum 60 mg/day for 3–10 days	■ Short courses or "bursts" are effective for establishing control when initiating therapy or during a period of gradual deterioration.
Prednisone	1, 2.5, 5, 10, 20, 50 mg tablets; 5 mg/cc, 5 mg/5 cc			■ There is no evidence that tapering the dose following improvement in symptom control and pulmonary function prevents relapse.
				■ Patients receiving the lower dose (1 mg/kg/day) experience fewer behavioral side effects (Kayani and Shannon 2002), and it appears to be equally efficacious (Rachelefsky 2003).
				■ For patients unable to tolerate the liquid preparations, dexamethasone syrup at 0.4 mg/kg/day may be an alternative. Studies are limited, however, and the longer duration of activity increases the risk of adrenal suppression (Hendeles 2003).
Long-Acting Beta$_2$-Agonists (LABAs)				■ **Should not be used for symptom relief or exacerbations. Use only with ICSs.**
Salmeterol	DPI 50 mcg/ blister	Safety and efficacy not established in children <4 years	1 blister q 12 hours	■ Decreased duration of protection against EIB may occur with regular use.
				■ Most children <4 years of age cannot provide sufficient inspiratory flow for adequate lung delivery.
				■ Do not blow into inhaler after dose is activated.
Formoterol	DPI 12 mcg/ single-use capsule	Safety and efficacy not established in children <5 years	1 capsule q 12 hours	■ Most children <4 years of age cannot provide sufficient inspiratory flow for adequate lung delivery.
				■ Each capsule is for single use only; additional doses should not be administered for at least 12 hours.
				■ Capsules should be used only with the inhaler and should not be taken orally.

*Dosages are provided for those products that have been approved by the U.S. Food and Drug Administration or have sufficient clinical trial safety and efficacy data in the appropriate age ranges to support their use.

Figure 13-7: Usual Dosages for Long-Term Control Medications in Children

Medication	Dosage Form	0–4 years	5–11 years	Comments
Combined Medication				
Fluticasone/ Salmeterol	DPI 100 mcg/ 50 mcg	Safety and efficacy not established in children <4 years	1 inhalation bid	■ There have been no clinical trials in children <4 years of age. ■ Most children <4 years of age cannot provide sufficient inspiratory flow for adequate lung delivery. ■ Do not blow into inhaler after dose is activated.
Budesonide/ Formoterol	HFA MDI 80 mcg/4.5 mcg	Safety and efficacy not established	2 puffs bid	■ There have been no clinical trials in children <4 years of age. ■ Currently approved for use in youths ≥12. Dose for children 5–12 years of age based on clinical trials using DPI with slightly different delivery characteristics (Pohunek et al. 2006; Tal et al. 2002; Zimmerman et al. 2004).
Cromolyn/Nedocromil				
Cromolyn	MDI 0.8 mg/puff	Safety and efficacy not established	2 puffs qid	■ 4–6 week trial may be needed to determine maximum benefit. ■ Dose by MDI may be inadequate to affect hyperresponsiveness. ■ One dose before exercise or allergen exposure provides effective prophylaxis for 1–2 hours. Not as effective as inhaled $beta_2$-agonists for EIB. ■ Once control is achieved, the frequency of dosing may be reduced.
	Nebulizer 20 mg/ampule	1 ampule qid Safety and efficacy not established <2 years	1 ampule qid	
Nedocromil	MDI 1.75 mg/puff	Safety and efficacy not established <6 years	2 puffs qid	
Leukotriene Receptor Antagonists (LTRAs)				
Montelukast	4 mg or 5 mg chewable tablet 4 mg granule packets	4 mg qhs (1–5 years of age)	5 mg qhs (6–14 years of age)	■ Montelukast exhibits a flat dose-response curve. ■ No more efficacious than placebo in infants 6–24 months (van Adelsberg et al. 2005).
Zafirlukast	10 mg tablet	Safety and efficacy not established	10 mg bid (7–11 years of age)	■ For zafirlukast, administration with meals decreases bioavailability; take at least 1 hour before or 2 hours after meals. ■ Monitor for signs and symptoms of hepatic dysfunction.
Methylxanthines				
Theophylline	Liquids, sustained-release tablets, and capsules	Starting dose 10 mg/kg/day; usual maximum: ■ <1 year of age: 0.2 (age in weeks) + 5 = mg/kg/day ■ ≥1 year of age: 16 mg/kg/day	Starting dose 10 mg/kg/day; usual maximum: 16 mg/kg/day	■ Adjust dosage to achieve serum concentration of 5–15 mcg/mL at steady-state (at least 48 hours on same dosage). ■ Due to wide interpatient variability in theophylline metabolic clearance, routine serum theophylline level monitoring is essential. ■ See next page for factors that can affect theophylline levels.

Key: DPI, dry powder inhaler; EIB, exercise-induced bronchospasm; HFA, hydrofluoroalkane (inhaler propellant); MDI, metered dose inhaler

Figure 13-8: Usual Dosages for Long-Term Control Medications in Children (Continued)

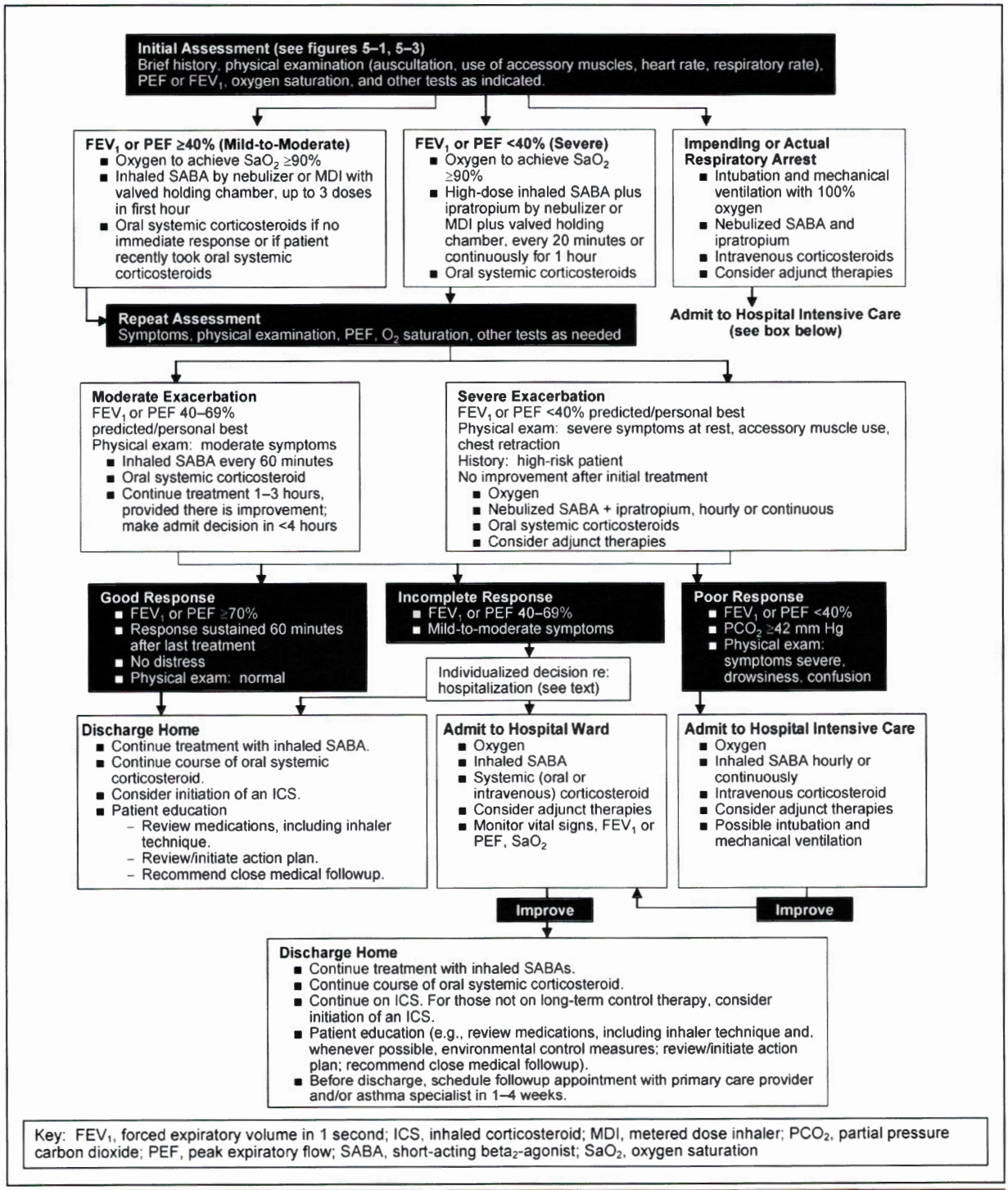


Figure 13-9: Management of Asthma Exacerbations: Emergency Department and Hospital-Based Care

MedStudy

PEDIATRICS BOARD REVIEW

PEDS

CORE CURRICULUM

5th EDITION

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GASTROENTEROLOGY & NUTRITION

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Gastroenterology & Nutrition

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NUTRITIONAL DEFICIENCIES

MARASMUS

Marasmus is severe calorie malnutrition in a child. These children have generalized loss of muscle and no subcutaneous fat. They appear to be very emaciated and cachectic. Linear growth is also affected if the malnutrition persists long enough. These patients have very loose wrinkled skin because of the loss of the subcutaneous fat. Facially, they have been described as having the look of a "wizened old man," due to the loss of temporal and buccal fat pads. Note that buccal fat pads are the last to go, indicating long-lasting, severe malnutrition. Because of the prolonged nature of inadequate energy stores, the body tries to adapt, and the child frequently has hypothermia, bradycardia, and hypotension.

KWASHIORKOR

Kwashiorkor is due to insufficient intake of protein. Frequently, it is also associated with an inadequate intake of calories. Kwashiorkor is an African term that means "the disease of the deposed baby when the next one is born." Typically, kwashiorkor appears in young children during the weaning or post-weaning process. Kwashiorkor is epidemic in developing countries, because the main calorie sources are carbohydrates that are low in protein—particularly white rice, cassava, and yams. This type of malnutrition can make a child appear fat, but this swelling is primarily edema; those affected are sometimes called "sugar babies."

These children present mainly with soft, pitting, painless edema, usually involving the feet and legs. In severe cases, it can extend to the face and upper extremities. Most affected children have skin rashes that can include hyperkeratosis and pigmentation changes due to desquamation of the epidermis. Their hair is dry and brittle and becomes yellowish-gray. In children who have fluctuating nutrition (some months good, other months poor), you may see a "flag sign" develop, which refers to areas of normal hair alternating with those of depigmented hair.

These children don't gain weight, but the failure to thrive (FTT) is masked by the edema. Their livers are usually large with fatty infiltration. T-cell function and cell-mediated immunity are not normal, and these children are at increased risk for infection.

PROTEIN-CALORIE MALNUTRITION (MARASMIC KWASHIORKOR)

Protein-calorie malnutrition has clinical features of both marasmus and kwashiorkor. The child presents with the severe edema of kwashiorkor and the cachexia of marasmus. It is the most common form of nutritional deficiency found in the U.S.

VITAMIN C DEFICIENCY (SCURVY)

Vitamin C (ascorbic acid) deficiency, or scurvy, is rare in the U.S. The majority of cases appear in children between 6 months and 2 years of age. Initial symptoms of vitamin C deficiency are nondescript and include irritability, digestive disturbances, and anorexia. Classic physical descriptions include follicular hyperkeratosis and "corkscrew-coiled" hairs. Gingival bleeding is also common. Normochromic, normocytic anemia is found in ~ 75% of patients with scurvy.

Vitamin C deficiency impairs the formation of collagen and chondroitin sulfate. The lack of collagen results in fragile capillaries and gingival hemorrhage; the lack of chondroitin sulfate results in osteoblasts no longer making osteoid, a process that causes the cessation of endochondral bone formation. In other words, bones become brittle and fracture easily. Most of the abnormalities are found at the metaphyseal zone of tubular bones and at the sternal-rib junctions. Since scurvy has been around for a while, it has numerous eponyms describing the x-ray findings:

1) White line of Frankel: a dense band at the growing metaphyseal end, involving the provisional zone of calcification (Image 14-1)
2) Wimberger ring: small epiphysis surrounded by a sharp, sclerotic rim
3) Trümmerfeld zone of lucency: a transverse band of radiolucency beneath the dense zone of provisional calcification
4) Pelkan spur: a marginal spur formation
5) Corner sign: suggestive of subphyseal infarctions

Treatment is oral ascorbic acid.

FAT-SOLUBLE VITAMIN DEFICIENCIES

Vitamins A, D, E, and K are fat-soluble vitamins and require carrier proteins for transport. They all require intact mechanisms for fat digestion and absorption for uptake. Vitamins A and D are transported by specific plasma proteins, and vitamins E and K are transported mostly by low-density lipoproteins (LDL). All of these vitamins are responsible for regulating protein synthesis. Deficiencies can result in complications frequently seen on Board exams.

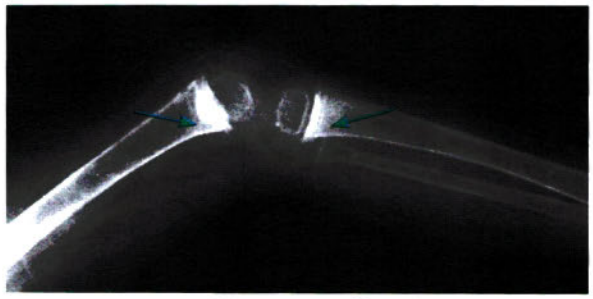


Image 14-1: Scurvy with White Lines of Frankel

Vitamin A requirements generally are in the 10–30 µg/kg range of body weight, but infants have a higher requirement. Typically, vitamin A deficiency results in night blindness, Bitot spots (keratinization of the cornea), xerophthalmia (dry eyes), corneal opacities, growth failure, increased susceptibility to infection, and even death. If you see a child with vitamin A deficiency on the exam, and that child has clouding of the cornea, this is a medical emergency that requires large parenteral doses of vitamin A. Excess vitamin A can result in scaly skin, pseudotumor cerebri, and hepatomegaly.

Vitamin D is necessary for bone growth and maturation. If not available, rickets can occur in children and osteoporosis/osteomalacia in adults (Image 14-2). Vitamin D levels are very low in breast milk, so exclusively breast-fed infants need to be supplemented with 400 IU of vitamin D daily. For older children with adequate exposure to light, vitamin D supplementation is usually not necessary, but, if needed, these children should receive 600 IU daily. Children at risk are those with limited sun exposure, especially those in northern and western countries where sunlight exposure is limited due to the bandwidth of radiation that can pass through clouds. Other risk factors include prematurity and darker skin. Rickets can present with poor growth, hypocalcemia, hypophosphatemia, and tetany. Skeletal deformations and bone pain can also occur. Table 14-1 lists possible manifestations of rickets.

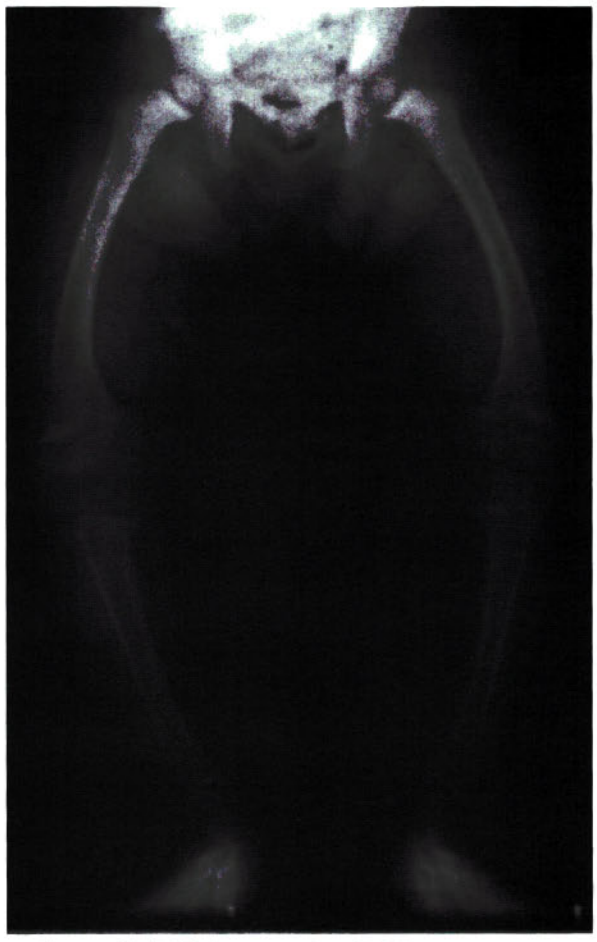

Michael L. Richardson, MD/Wikimedia

Image 14-2: Skeletal Deformation from Rickets

However, be aware that the most frequent presenting clinical finding of rickets in infants and children is "nothing"—it is most frequently diagnosed through an incidental finding on physical examination.

Laboratory may show:

- ↓ Calcium (but can be normal until late)
- ↓ Phosphorus (but can be normal until late)
- ↑ Alkaline phosphatase
- ↓ 25-(OH) vitamin D_3 levels (this is the level that is commonly done to initially test for overall vitamin D status)
- 1,25-$(OH)_2$ vitamin D_3 levels can be ↓, ↑, or normal
- ↑ Parathyroid (PTH) hormone levels

So, look for a high PTH, low 25-(OH) D_3, and a high alkaline phosphatase level. The high PTH is indicative of the hormonal response that tries to maintain normal calcium.

Diagnosis of rickets is usually made by radiographic examination of the long bones, which show rarefied shafts and uneven, blurred ends. Once vitamin D treatment is started, the long bone ends will "brighten" on x-ray.

Vitamin E (also known as tocopherol) functions as a membrane-bound antioxidant by inhibiting free radical-catalyzed lipid peroxidation and terminating radical chain reactions. Thus, it serves to protect the body from biologic processes that damage cellular and intercellular structures.

Table 14-1: Manifestations of Rickets

Bone pain or tenderness:
Arms, legs, spine, and pelvis
Skeletal deformities:
Bowlegs
Forward projection of the breastbone ("pigeon chest")
Enlargement of the costochondral joints in the rib cage ("rachitic rosary")
Asymmetrical or odd-shaped skull and craniotabes ("ping-pong ball" consistency)
Spine deformities (including scoliosis and kyphosis)
Pelvic deformities
Increased tendency toward bone fractures
Dental deformities:
Delayed formation of teeth
Defects in the structure of teeth, holes in the enamel
Increased incidence of cavities
Muscle cramps and weakness
Impaired growth
Short stature

Quick Quiz

- What is marasmus? How does marasmus differ from kwashiorkor?
- What are the manifestations of rickets?
- What vitamins and minerals must be supplemented in a strict vegan diet?

Vitamin E deficiency can result in neurologic dysfunction, especially neuroaxonal degeneration and loss of reflexes. In the preterm infant, vitamin E deficiency may present with hemolytic anemia. Vitamin E deficiency is especially common in children with fat malabsorption and is seen particularly in children with cystic fibrosis.

Vitamin K is necessary for maintaining prothrombin, Factor VII, Factor IX, and Factor X. Most vitamin K is obtained in foods, such as dark leafy vegetables, cauliflower, and soybeans. Another non-dietary source is bacterial synthesis in the gut. Vitamin K deficiency is uncommon once the intestinal flora is established, except in children with malabsorption, as seen in cystic fibrosis, ulcerative colitis, or history of intestinal resection. Therefore, it is most common in these children or in newborns and infants who have not yet developed significant bacterial gastrointestinal flora. As a result, it is routine to give vitamin K prophylaxis at birth (0.5–1 mg IM or 1–2 mg orally). Antibiotic use in the newborn or infant may also "sterilize" the intestinal flora, resulting in vitamin K deficiency. Additionally, certain cephalosporins (moxalactam, cefamandole, cefoperazone, cefotetan, and cefmetazole) impair recycling of vitamin K and can result in hypoprothrombinemia.

FOLATE DEFICIENCY

Folate is a water-soluble vitamin and is not stored, so you must have constant intake. Deficiency is associated primarily with hematological problems, including leukocyte and cellular immune dysfunction. Folate deficiency is the #2 nutritional cause of anemia (iron is #1)! Think folate deficiency and fat RBCs (high MCV). Look for it on the Board exam in an infant or child who drinks goat's milk. Also know that folate deficiency in the pre-pregnant and pregnant woman increases the risk of neural tube defects.

OTHER VITAMIN / MINERAL DEFICIENCIES

What the ABP could test you on:

- Thiamin (B_1) deficiency is associated with beriberi: paraesthesias, foot and wrist drop; and it is associated with Wernicke encephalopathy: ophthalmoplegia, ataxia, and confusion.
- Riboflavin (B_2) deficiency is associated with cheilosis and sore tongue.
- Niacin (B_3) deficiency is associated with pellagra: dermatitis, dementia, and diarrhea.
- Pyridoxine (B_6): In infants, seizures that respond to B_6 are associated with a metabolic defect.
- Cobalamin (B_{12}) deficiency is associated with megaloblastic anemia.
- Zinc deficiency can occur in any chronic diarrhea. Zinc-containing enzymes are involved in nucleic acid and protein metabolism, so zinc deficiency will affect rapidly growing cells. These patients "don't grow" and have diarrhea, a rash (acrodermatitis enteropathica), and hypogeusia (reduced taste).

VEGETARIAN DIETS

Vegetarianism is an acceptable diet for children and other groups as long as appropriate supplements are included (for strict vegans: vitamin B_{12}, iron, calcium, and zinc). Groups especially at risk are infants, children, and pregnant and lactating women. Risks are minimal with a "semi-vegetarian" diet, such as one that includes eggs and milk and/or non-red meat in the nutritional regimen.

Vegetarians can be classified based on the types of protein individuals are willing to consume. All vegetarians leave red meat out of their diets, but pollo-vegetarians eat poultry, pesco-vegetarians eat fish and other seafood, and lacto-ovo-vegetarians eat milk, dairy products, and eggs (but no seafood or meats). The total vegetarian, known as a vegan, will not eat any food of animal origin and eats only foods that are of plant origin. For children, this strict of a regimen can make it hard to meet daily caloric and nutrient requirements. Typically, vegans must be sure to include nuts, seeds, or grains that contain methionine, and legumes that contain lysine, to meet daily requirements of these essential amino acids.

Strict vegans must supplement their diet with vitamin B_{12}, which is of animal origin only. The supplement can be in the form of vitamins packaged as such, or else vitamin-fortified cereal, yeast, or soy milk. Breastfed infants of mothers who are marginally deficient in B_{12} also are at marked risk for B_{12} deficiency.

Iron is another problem area for the strict vegan child. Iron from plant sources (nonheme iron) is much less absorbed than from animal-derived iron (heme iron). Co-administering iron-containing foods with vitamin C can enhance the absorption of iron.

Calcium is another element that is of concern for the strict vegan. Calcium-fortified soy milk and calcium-fortified juices can provide the daily requirements. Many vegan diets also lack vitamin D; sunlight exposure can help the body synthesize this vitamin.

Zinc deficiency is relatively common in strict vegans; thus, zinc frequently must be supplemented as well.

FLUIDS AND ELECTROLYTES

Many methods are available to treat and diagnose fluid and electrolyte abnormalities. Most are based on body weight and include the basal calorie method, the surface area method, and the Holliday-Segar formula. The first two methods require tables, while the latter formula can be used to answer Board questions on dehydration.

The Holliday-Segar formula for daily kcal required under basal conditions is:

100 kcal/kg for the first 10 kg plus

50 kcal/kg for the next 10 kg plus

20 kcal/kg for the rest of the weight

Example: For a 23-kg patient, the total kcal required per day is:

(100 x 10) + (50 x 10) + (20 x 3)

or

1,000 + 500 + 60 = 1,560 kcal per day

See Table 14-2 for more on the Holliday-Segar formula. Note that the 3rd column further looks at kcal per hour.

How do you clinically assess dehydration in infants/young children (Table 14-3)?

Note that rehydration guidelines have changed and IV therapy is no longer standard treatment for most dehydration scenarios; instead, oral rehydration solution is recommended.

For mild dehydration, 50–60 mL/kg of an oral rehydration solution (ORS) is recommended. At the level of moderate dehydration, 80–100 mL/kg of ORS is prescribed. For severe dehydration, a fluid infusion of normal saline or lactated Ringer's at 40 mL/kg/hr until the pulse and consciousness are normal is recommended. The patient then completes rehydration with 50–100 mL/kg of ORS.

Table 14-2: Holliday-Segar Formula for Maintenance of Calories and Fluids

Weight	kcal/d or mL/d	kcal/h or mL/h
0–10 kg	100/kg/day	4/kg/hour
11–20 kg	1,000 + 50/kg/day*	40 + 2/kg/hr*
> 20 kg	1,500 + 20/kg/day**	60 + 1/kg/hr**

* for each kg > 10 ** for each kg > 20

Table 14-3: Dehydration

Clinical Data	Severity of Dehydration	Estimated Weight Loss	mL/kg
Dry mucous membranes Oliguria	Mild	5%	50
Marked oliguria Poor skin turgor Sunken fontanelle Tachycardia	Moderate	10%	100
Hypotension Poor perfusion	Severe	15%	150

VOMITING

OVERVIEW

Vomiting, by itself, is a presentation for many disorders, from viral gastroenteritis to otitis media to small bowel obstruction. Vomiting is a coordinated motor response of the GI tract, abdominal muscles, and thoracic muscles, resulting in the forceful expulsion of stomach contents. (Yum!) Nausea precedes retching, which precedes emesis.

The vomiting center is located in the nucleus solitarius and a series of nuclei in the medulla of the brainstem. Stimuli to these areas can come from the posterior pharynx (gagging), the GI tract (distention), and the brain (dizziness). Also, the chemoreceptor trigger zone, which is located in the floor of the 4th ventricle, receives stimuli from apomorphine, opiates, cytotoxins, ammonia, etc.

Some associations can be helpful in suggesting the possible etiology:

- Bilious: GI obstruction
- Blood: upper GI bleed
- Fever: gastroenteritis or systemic infection
- Emesis only, effortless without nausea or retching: GE reflux
- Undigested food: achalasia or delayed gastric emptying
- Projectile emesis: pyloric stenosis, antral web, annular pancreas
- Tense fontanelle: increased intracranial pressure due to meningitis or tumor
- Older adolescent female: pregnancy, drugs, migraine, bulimia

CHRONIC VOMITING

In cases of chronic vomiting when clues are not helpful in delineating a cause, proceed with an abdominal ultrasound and then a stepwise evaluation that may include upper gastrointestinal contrast x-rays or endoscopy. In one study, children with vomiting for over a month were evaluated, and a "histologic" diagnosis was made in about 60% of the cases. The main causes were esophagitis and gastritis (including *Helicobacter*-induced). Less commonly found (< 5%) were duodenitis and giardiasis. Endoscopy is the best test for diagnosis of chronic vomiting.

Quick Quiz

- What are the basal kcal/day requirements for a 17-kg child? A 31-kg child?
- An 11-kg baby comes in with vomiting. What does bilious vomiting suggest?
- What does vomiting undigested food indicate?
- What is cyclic vomiting?
- The finding of currant jelly stool indicates what possible diagnosis?
- Name clues useful in diagnosing functional abdominal pain.
- Name clues that indicate an organic cause for abdominal pain.

CYCLIC VOMITING

Cyclic vomiting occurs with paroxysms of vomiting followed by intervals of complete health. It is most commonly seen in girls between the ages of 6 and 7. These girls develop intense vomiting episodes that last from hours to days, with vomiting as often as 6 times/hour. The "well spells" last from several weeks to many months between episodes. There is a strong association with a family history of migraine headaches.

Think about the diagnosis when the history is characteristic and the physical examination is normal. You then must evaluate for any plausible organic disease.

Consider the following: metabolic screening during an attack; an upper GI with small bowel follow-through; endoscopy with biopsies; and brain imaging.

Treatment can be difficult. Prophylactic use of propranolol, amitriptyline, phenobarbital, cyproheptadine, and erythromycin has been tried. Newer agents, including ondansetron and nasal sumatriptan, are in trials.

ACUTE ABDOMINAL PAIN

HISTORY / PHYSICAL / LAB

Acute abdominal pain is a common complaint in children who present to parents, school nurses, and emergency rooms. Less than 5% who present to emergency rooms require admission for observation or surgery. It can be very difficult to differentiate the emergencies from the non-emergencies. Usually, careful history and repeated physical examination are most important in delineating the etiology. Supplement your investigation with laboratory and diagnostic studies as appropriate to confirm normalcy.

Some clues in the history can be helpful for acute abdominal pain:

- Presenting with the acute onset of pain as the first symptom: intussusception, midgut volvulus, ovarian torsion
- Trauma: perforated viscus, hemorrhage, musculoskeletal injury, pancreatitis
- Bilious vomiting: intussusception, volvulus, incarcerated hernia, adhesions
- Peritonitis: appendicitis, cholecystitis, PID
- Adolescent female: PID, pregnancy, ectopic pregnancy, ovulatory pain (mittelschmerz)
- Currant jelly stool: intussusception
- Melena: upper GI bleed
- No specific finding: gastroenteritis, toxins, UTI, pneumonia (when cough is in the history), functional abdominal pain

Initial laboratory studies for a child with acute abdominal pain include a CBC, U/A, and (for the adolescent female) pregnancy test. These are relatively nonspecific (well, except for the pregnancy test!). If the history and physical examination are "classic" for appendicitis, perform surgery. Abdominal x-rays can show obstruction, calcification, ischemia, or free air. You can rule out pneumonia or pneumothorax with chest x-ray.

Perform ultrasound and/or CT scan in patients who don't improve over several hours and who don't have defining peritoneal signs.

FUNCTIONAL ABDOMINAL PAIN

Functional abdominal pain is essentially one of the more difficult diagnoses to deal with in children. School absenteeism is a major problem in nearly 1/3 of children with functional abdominal pain.

Clues for diagnosis of functional abdominal pain [Know these!]:

- Pain occurs longer than 3 months.
- Age of onset between 6 and 14 years of age.
- Child exhibits features of abdominal pain (grimacing, guarding abdominal muscles, rubbing painful areas).
- Physical and psychological stressors exacerbate the pain.
- Normal physical examination with no significant weight loss.
- Stool occult blood exam is negative.
- Normal laboratory testing (CBC, ESR, U/A, stool ova and parasites).

Clues that indicate an organic cause for the abdominal pain [Know these!]:

- Pain awakens the child at night.
- Pain is localized or persistent away from the umbilicus.

- Weight loss or FTT.
- Fever, rash, joint pain, mucous membrane changes/ulcers, dysuria.
- Sleepiness following painful attacks.
- Guaiac-positive stools.
- Anemia.
- Elevated ESR.
- Family history of peptic ulcer disease or inflammatory bowel disease.

Treat functional abdominal pain with reassurance and education. Pain resolves within 2 weeks in 30–50% of patients after they are diagnosed! Frequently, those who don't resolve have recurrent pain into adulthood, but it does not limit daily activities in most of these adults.

ACUTE DIARRHEA

HISTORY / WORKUP

Acute diarrhea is defined as lasting less than 14 days. Almost all diarrhea in children is due to an infectious disease agent. For most, aim therapy at rehydration and providing nutritional needs. You do not need to search for an etiologic agent since most are self-limited.

Certain things, though, should prompt you to do further evaluation:

- Infants < 2 months of age
- Gross blood in the stool
- WBCs on microscopic exam of the stool
- Toxic-appearing child
- Immunocompromised child
- Diarrhea developing while an inpatient or following a course of antibiotics

If one or more of these are present, order further stool studies to look for invasive bacterial infection. The infant younger than 2 months requires special care because of the risk of quickly developing dehydration, as well as the many noninfectious etiologies that appear in this age group. Depending on your suspicions, stool studies can include a rotavirus ELISA; stool cultures for *Salmonella*, *Shigella*, *Campylobacter*, *Yersinia*, *E. coli* O157:H7, *Aeromonas*, etc.; *C. difficile* toxin; and *Giardia* or *Cryptosporidium* assays with ova and parasite preps.

ORAL REHYDRATION THERAPY

Treat acute diarrhea with oral rehydration therapy. Commercial formulations are available and include Infalyte®, Pedialyte®, and Rehydralyte®, as well as generic products. These are formulated to be iso- or hypotonic with appropriate amounts of electrolytes. Note: Do not recommend using "clear" liquids with these products. Most "clear" liquids (juices, soft drinks, Gatorade®) are hypertonic and have excess glucose. These will often result in ongoing diarrhea-like stools even after the illness has resolved.

Certain contraindications to oral replacement therapy that you should know:

- Shock (as initial therapy)
- Stool output > 10 mL/kg/hour
- Ileus
- Monosaccharide intolerance

In patients with these manifestations, you will likely need to initiate intravenous therapy.

Note: Vomiting is not a contraindication to using oral replacement therapy and does not reduce its success rate. The recommended course with these patients is a clinical trial of oral rehydration.

FEEDING DURING ACUTE DIARRHEA

After rehydration has been achieved, resume the child's diet. The traditional "bland" diet results in a longer recovery time and has actually never been validated in a clinical trial. Breastfed infants should resume breast-feeding. Infants on solid foods can resume their normal diets. Avoid high-sugar foods, such as juices, which can result in osmotic diarrhea. Also recommend feeding small amounts at frequent intervals.

Children who are on cow's milk or commercial milk formulas can resume their diets, although a small number will develop acidosis or recurrent diarrhea. If this occurs, withhold milk/formula for 1–2 days, temporarily using instead a lactose-free formula. There is a higher incidence of transient lactose intolerance in very young infants.

USE OF ANTIDIARRHEAL AGENTS

Antidiarrheal agents are widely available over the counter and by prescription. The most commonly used agents are known as "absorbents." These include magnesium aluminum silicate, which is found in over-the-counter brands Donnagel® and Kaopectate®, as well as generic forms. They mainly alter stool consistency and do not affect absolute fecal water loss, but they do give the illusion that the diarrhea is better. Bulk-forming agents (methylcellulose, psyllium seed, soy fiber) are also "absorbents" and work similarly to the silicate products. Although the stools appear more normal, they do not shorten the length of the infection.

Antimotility drugs are another type of agent. Generally, these are opiates, such as codeine, diphenoxylate, or loperamide. They can be quite dangerous in children; thus, do not use routinely. Opiates can induce ileus and worsen underlying bacterial infections.

The third type of available antidiarrheal is probiotics. These are microorganisms that may be taken to modulate diarrhea that is due to bacterial or viral etiologies. *Saccharomyces boulardii* is a nonpathogenic yeast,

QuickQuiz

- What is the most common cause of diarrhea in children?
- Should most diarrheas be treated with oral or IV therapy?
- Do children with resolving diarrhea require special diets?
- What causes the majority of constipation?
- Is it rare for a breastfed infant to pass a stool less often than once every 5 days?
- What is the most common nonorganic cause of constipation?

which is helpful in reducing the recurrence rate of *Clostridium difficile* diarrhea. Studies have shown that *Lactobacillus GG* (previously known as *L. rhamnosus*, sold as Culturelle®) lessens the severity of rotavirus infection.

The fourth main group of agents is the antisecretory agents. These include somatostatin and octreotide. They act by stimulating sodium and chloride absorption and inhibiting chloride secretion. These cannot be administered orally and are utilized only in special clinical situations.

Finally, a special type of agent is bismuth subsalicylate (Pepto-Bismol® and Kaopectate®). Bismuth has both antimicrobial and antisecretory properties; it also contains magnesium aluminum silicate, which is an absorbent. Warn parents that this agent will result in dark black stools.

CONSTIPATION

DEFINITION

Constipation has no standardized definition and varies from person to person. Note that constipation is a symptom and not a disease or sign. Only a very small minority of children who present with constipation will have an organic or anatomic cause. A majority of constipation is due to a functional or behavioral problem. Early on, it is more common in boys, but by adolescence, it is more common in girls.

Some breastfed infants will pass a stool only once every 5–10 days; in the absence of other signs or symptoms, they do not need treatment. Some older children will pass a stool only every 3–4 days; they do not have any other symptoms, and this pattern continues into adulthood. Image 14-3 shows an intestinal pattern "full of stool."

"THEY STRAIN WHEN THEY POOP" SYNDROME

A common presentation of infants during the first 10 weeks of life is a parent who comes in and says, "My child strains all the time and cries before every bowel movement." This is perfectly normal because some infants have difficulty coordinating an increase in intraabdominal pressure and relaxation of the pelvic floor at the same time. These cries, grunts, and facial expressions are all an effort to get this coordination down. For this reason, **do not use or recommend enemas or suppositories for these infants**! The recommendation for these infants is parental reassurance.

FUNCTIONAL FECAL RETENTION

Functional fecal retention (aka psychogenic constipation) is the **most** common nonorganic cause of constipation. It is also responsible for encopresis in most children. The fecal retention is due to voluntary "withholding" of stool secondary to the fear of defecation. The disorder occurs at two peaks: toilet-training time and the start of school. It also may develop before toilet training has even been attempted. Causes of the disorder during the toilet-training period are: training at an inappropriately young age, obsessive attitudes toward rectal incontinence, and extreme pressure put on the child to "avoid accidents." Some children also have had past experiences with painful defecation, anal fissures, or perianal infections, all of which can cause discomfort to the point that they learn to equate defecation with pain. Also consider child sexual abuse as an etiology if the retentive constipation is a new, sudden onset.

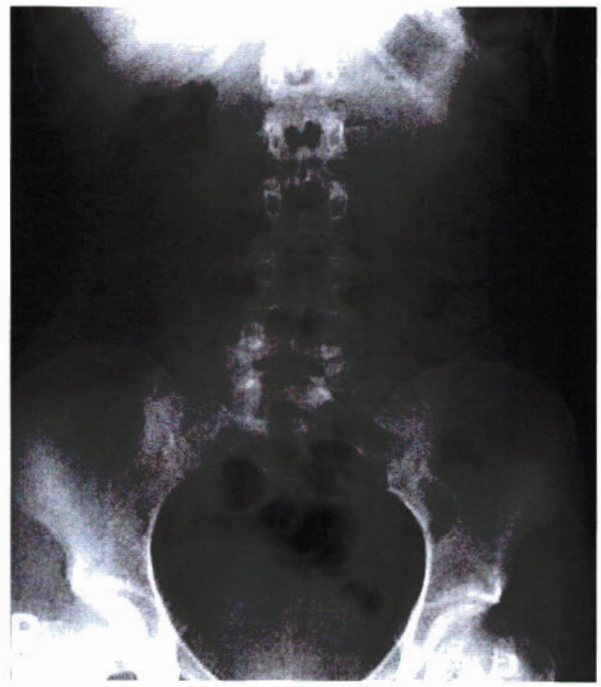


Image 14-3: PA Abdominal X-ray, FOS

The whole cycle begins with the child voluntarily "holding in" a bowel movement. This accumulates in the rectum, and the child must increasingly contract the pelvic floor muscles and buttocks to prevent stool from passing. As the stool continues to amass, the child's mood and appetite are adversely affected, and the child may experience abdominal pain. Soiling frequently occurs when the child has flatus, because the child cannot keep all of the rectal contents intact. The withholding cycle is reinforced when the parent becomes angry at the child for soiling, and the child is actually already trying to prevent any stool passage. Eventually, many develop a negative self-image.

It is important to differentiate functional constipation from other etiologies. This is usually fairly easy to do. Hirschsprung disease will not usually present with fecal soiling, and the rectal vault will be empty instead of full of stool. Physical examination will show anal fissures or evidence of sexual abuse on the anal area. The finding of a vascular or pigmented hairy patch on the sacrum suggests spinal dysraphism.

Treatment of functional constipation requires a mixed behavioral and medical approach, including positive reinforcement schedules and the use of stool softeners. Usually, some sort of "clean-out" of the fecal bolus is required, sometimes with enemas. Occasionally, prokinetic agents are needed and, in very rare instances, surgical interventions. Give stool softeners to make stool passage painless, and instruct parents to make sure the child has unhurried time on the toilet 2–3 times a day after meals. The child should sit on the toilet with feet pressed firmly against the floor (or a footstool, if necessary) to help with defecation. Once the fecal mass is cleared, maintenance therapy is necessary to allow the cycle of withholding to be broken. Most commonly used agents include polyethylene glycol, mineral oil, and lactulose. Titrate doses up or down to reach the desired results. After at least 6 months of pain-free and accident-free success, discontinue the agents. Failure rates approach 20% regardless of the treatment used. Relapses are also common in children that were treated for this previously. Avoid excessive oral phosphates and hypertonic enemas.

ESOPHAGUS DISORDERS

TRACHEOESOPHAGEAL FISTULA AND ESOPHAGEAL ATRESIA

Overview

Tracheoesophageal fistula and esophageal atresia occur in about 1/4,000 live births. Nearly 90% of tracheoesophageal abnormalities present as a blind, upper esophageal pouch with a fistula between a lower esophageal segment and the lower portion of the trachea, near the carina. The next most common abnormalities include esophageal atresia alone with two blind pouches (the esophagus is closed distally, and the stomach is closed proximally, without a connection between the two) and an "H-type" tracheoesophageal fistula, which has a connection between a normal esophagus and a normal trachea. Esophageal stenosis alone can also occur. A clue for esophageal abnormalities can occur prenatally, with the presence of polyhydramnios in about half of the mothers during their pregnancy.

Know that nearly 1/3 of these infants will also have other congenital anomalies. The most common association is known by an acronym: VACTERL (Vertebral, Anal atresia, Cardiac [PDA, ASD, VSD], TracheoEsophageal fistula, Renal [urethral atresia with hydronephrosis], and Limb anomalies [humeral hypoplasia, radial aplasia, hexadactyly, proximally placed thumb]).

Esophageal Atresia with Distal Tracheoesophageal Fistula

Esophageal atresia with distal tracheoesophageal fistula is the most common form of anatomical esophageal abnormality. Look for this in the delivery room or early in the nursery. The infant will present with excessive oral secretions and appear to be choking frequently. Diagnose by trying to place an NG tube into the stomach, whereupon the blind pouch of the esophagus would then prevent passage. A simple x-ray of the chest will show the abnormality fairly well—look for a dilated proximal esophagus with air distention of the entire gastrointestinal tract.

See Image 14-4 and Image 14-5. The catheter tip stops in the blind pouch of the esophagus.

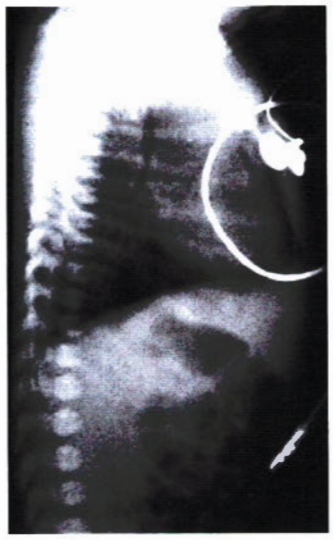


Image 14-4: Lateral, Eso. Atresia

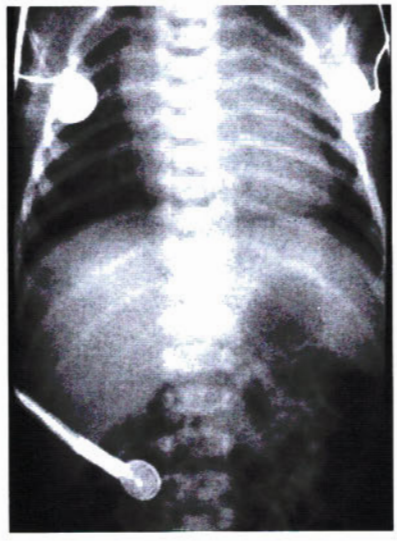


Image 14-5: PA, Eso. Atresia

QuickQuiz

- How do 90% of tracheoesophageal abnormalities present?
- What does VACTERL stand for?
- At the bedside, how do you diagnose esophageal atresia with distal tracheoesophageal fistula?
- What is achalasia?
- True or false? Achalasia in infancy is due to a congenital disorder.
- Is GE reflux a normal process for many infants?

Initially in these infants, place an orogastric catheter into the blind pouch and tape it into position, then connect it so that there is continuous drainage of the saliva from the pouch to prevent aspiration. Also, it is important to keep the head elevated at about 30 degrees, which will prevent stomach contents from being refluxed back into the trachea. After a cardiac evaluation rules out potential cardiac abnormalities, perform surgery as soon as possible.

Optimal treatment is to reanastomose the esophagus and close off the fistula. In a very ill or very small infant, this may be delayed by doing a gastrostomy and waiting until the child is well enough to perform the definitive surgery. The main complication of surgery is the leakage of material through the anastomosis area. An anastomotic leak can present as tachypnea and a sepsis-like picture on the 3rd to 4th day after surgery. Another complication is stricture formation. GE reflux is increased in these patients after the surgical changes required to pull together the esophagus are completed.

Esophageal Atresia without Tracheoesophageal Fistula

Babies born with isolated esophageal atresia have excessive oral secretions with choking and also a flat, gasless abdomen, which is not seen in those with a tracheoesophageal fistula. These infants usually have a very wide gap between the two ends of the esophagus, so primary anastomosis is less likely to be an option. Usually, esophageal lengthening, done by bougienage or magnets (!), will work only if the gap is less than 3–4 cm. If the gap is > 4 cm, esophageal replacement is necessary. This is generally delayed until after one year of age. In this procedure, you bridge the gap with a gastric tube, a colon segment, or a small intestinal segment.

Tracheoesophageal Fistula without Esophageal Atresia (The H-type Fistula)

Infants with the H-type fistula may present in early infancy with choking during feeding. Others will present later with cough, pneumonia, or reactive airway disease. This variant is not associated with maternal polyhydramnios. Diagnosis is tricky; barium swallows will frequently miss the H-type fistula. You may need to perform an esophagoscopy and/or bronchoscopy to confirm the diagnosis. Surgery to tie off the fistula is curative. Occasionally, this type of fistula has presented in adults without prior knowledge of their congenital abnormality.

Esophageal Stenosis and Web Diaphragms

Esophageal stenosis and web diaphragms are both rare. They present as dysphagia when solids are introduced to a child. Diagnose with barium swallow or endoscopy. Usually, either can be treated by dilation. A special case is stenosis due to ectopic cartilage known as tracheobronchial remnants. Remove this surgically because it has a high risk of perforation.

ACHALASIA

Achalasia is a disorder of the esophagus caused by incomplete relaxation of the lower esophageal sphincter (LES) and a lack of normal esophageal peristalsis. Thus, it is a motor problem, not an anatomic problem. Patients present with difficulty swallowing (dysphagia), regurgitation, recurrent pneumonia, weight loss, and chest discomfort. Achalasia appears to be due to loss of ganglion cells in the esophagus and to dorsal motor nuclei reduction of the vagus nerve. Many patients have antibodies to the Auerbach plexus. Only about 5% of all achalasia cases occur in children; the average age for presentation in children is 9 years.

If it presents in infancy or early childhood, it is likely due to a congenital disorder. One such genetic syndrome is known as Allgrove (or triple-A) syndrome, which associates achalasia with alacrima and adrenal deficiency. Another rare genetic syndrome is autosomal recessive, with deafness, vitiligo, short stature, and muscle weakness.

Treat achalasia with pneumatic balloon dilation of the LES. Although botulinum toxin injections work well in adults, this therapy requires repeated injections and, thus, is less often used in children. Occasionally, surgical intervention with an LES myotomy is required.

GE REFLUX (GER) AND GE REFLUX DISEASE (GERD)

GER VS. GERD

GE reflux (GER) is defined as return of gastric contents into the esophagus. This is actually a normal process, and it becomes spitting up or vomiting if the refluxed material passes out the mouth. This is normal? Well, yes. 1/2 of infants 0–3 months of age vomit at least once daily, and 2/3 of those 4–6 months old do too! This decreases rapidly after 8 months of age. Most infants

with daily vomiting outgrow this problem by 2 years of age and do not require special treatment.

In a small percentage of infants, though, GE reflux may become GE reflux disease (GERD). GERD can manifest as FTT due to the inability to consume and maintain enough calories in the digestive tract. There may also be esophageal symptoms with pain, inflammation, and bleeding, or airway symptoms with hoarseness, laryngitis, cough, pneumonia, and apnea. The only obvious clinical symptom may be irritability, but this can be from a variety of causes. GERD is rare in normal children; however, it is commonly seen in children with disabilities. In infants and children without adequate airway protective measures, GER or GERD is more likely to cause airway complications, such as aspiration pneumonia or reactive airway disease exacerbations.

Diagnosis

Diagnosis of GERD is difficult, and there is no absolute test that defines it. An upper GI exam is often one of the first tests done in a vomiting infant. It can show anatomic abnormalities in the vomiting child, such as pyloric stenosis, esophageal stricture, and antral webs. It can also show evidence of esophageal motility problems like achalasia. What it doesn't do is diagnose GER, because—remember—normal children have reflux too. So the upper GI is good for showing anatomic or motility problems only.

You can use a pH probe to record the duration and number of acid reflux episodes that occur in an infant or child. The test is helpful for determining the risk of esophagitis. If the infant has > 12% in a 24-hour period with decreased pH as detected by the probe, that infant is at increased risk of esophagitis. > 6% is the cutoff in older children. A normal pH probe study does not exclude GER. A positive test also does not always mean that recurrent wheezing or pneumonia is due to the GER detected; it just increases the likelihood that GER is a contributing factor.

Upper endoscopy with biopsy of the esophagus can be diagnostic for esophagitis. This procedure can also be used to diagnose other diseases, such as Crohn disease or infectious causes of esophagitis.

Nuclear scintigraphy is another test that can show where formula or food goes after normal feeding. In this case, an isotope-labeled formula or food is given in the normal fashion, and then the patient is monitored for episodes of GER for about an hour after feeding. Remember again, it is normal to have GER, so it is diagnostic only if food material is seen going into the lungs. This indicates that airway protective measures are defective, and the child is at serious risk for aspiration. You also can use scintigraphy as part of an emptying study to measure the motility of the stomach, which can be responsible for delayed vomiting.

Treatment of GER

Since most infantile GER is normal, direct initial therapy toward parental reassurance. For those parents who are upset or having difficulty dealing with the vomiting child, suggest thickening the formula with rice cereal, using 1–2 tablespoons per ounce of formula. The problem with this is that since the thickened formula frequently will not get through the nipple correctly, the parent will have to cut the nipple. This may increase the cough or feeding problems the infant is already having. Do not encourage prone sleeping because of the definite increased risk of SIDS in babies who sleep in the prone position. Also, do not give medications to infants with uncomplicated GER. The recent guidelines on GER also recommend a 2-week trial of a low-allergy formula due to the common occurrence of reflux in children with formula protein allergy.

You must rule out other causes in infants with GER who have poor weight gain. If no other causes are found, therapy is indicated. You can suggest food thickening and/or increasing the caloric content of food. If this is unsuccessful, do a trial of medical therapy. On rare occasions, the vomiting may be so severe that the infant will require NG feedings or postpyloric feedings. Do not recommend surgery for children when GER is the etiology for their poor weight gain. If there is delayed stomach emptying, promotility therapy may be helpful.

Treat esophagitis with an antisecretory agent, such as an H_2-receptor blocker (ranitidine, famotidine, etc.) or proton pump inhibitor (omeprazole). If esophagitis is severe and prolonged for many years without therapy, the esophagus can develop strictures, or Barrett esophagus can occur. Barrett esophagus presents with intestinal metaplasia in the distal esophagus. Barrett esophagus is a premalignant condition requiring surveillance endoscopies and biopsy every 3–5 years. Barrett esophagus is rare in children and normally seen in the context of an underlying neurological difficulty or esophageal anomaly.

Aggressively treat asthma, recurrent pneumonia, and laryngeal signs/symptoms due to GER with a proton pump inhibitor. Anti-reflux surgery is usually not indicated unless the symptoms cannot be controlled with medications.

Treatment of GERD

Treatment of GERD is initially aimed at dietary measures and positioning. The dietary measures include providing small meals and thickened feeds, while also avoiding carbonated drinks, high-fat foods, acidic foods, caffeine, and nicotine (usually secondhand in children). Elevation of the head of the bed is useful. Avoid bedtime snacks and treat obesity.

If these measures are not effective, or if the disease is more severe or urgent, pharmacologic therapy is the next step.

QuickQuiz

- What is the initial treatment for GER?
- What is the initial treatment for GERD?
- Which children are at risk for having infection of the esophagus?
- How long after ingestion of a caustic substance should upper endoscopy be performed?

Acid secretion reduction is done best with H_2-receptor blockers or proton pump inhibitors (PPIs). Most believe that the PPIs are superior to the H_2-receptor blockers, and many recommend just using PPIs, although some insurers require failure of H_2 blockers before covering the greater expense of PPIs. Do not use antacids, especially the aluminum-containing compounds, because they can cause toxicity. Bethanechol and metoclopramide are both prokinetic drugs, but neither has been shown to be effective in the treatment of GERD.

Surgical therapy is the final option, especially for those children with severe respiratory or neurologic disease. The most commonly used procedure is the Nissen fundoplication. In this operation, the fundus of the stomach is pulled up and wrapped around the lower esophagus. The parts of the stomach that are wrapped around the lower esophagus are then attached together to form a "valve." The operative mortality from Nissen fundoplication is about 1%. You can now perform this procedure laparoscopically with reduced morbidity.

Recent adult studies have shown that prolonged medical therapy is more cost-effective and has lower morbidity.

EOSINOPHILIC ESOPHAGITIS

This disorder has been described with increasing frequency in the pediatric population. The symptoms may appear very similar to GER with epigastric pain, vomiting, or dysphagia. The diagnosis is made by endoscopic biopsy of the esophagus demonstrating infiltration of the lining with eosinophils. The current studies indicate this is an allergic process.

Treatment is controversial currently with some advocating the use of amino acid-based formulas for dietary avoidance, and others, the use of topical steroids.

INFECTIONS OF THE ESOPHAGUS

Infections of the esophagus are rare in children, except for those who are immunocompromised. Generally, those children at risk are those with HIV, DM, cancer, and long-term, high-dose steroid usage.

Candida, CMV, and HSV are the most common organisms to cause infection in the esophagus. Dysphagia is the most common symptom with which children present. Odynophagia (pain with swallowing) and retrosternal burning are also seen. Diagnose by endoscopy with biopsy and brushings for culture. Treat *Candida* with fluconazole, CMV with ganciclovir and/or foscarnet, and HSV with acyclovir.

HOUSEHOLD INGESTIONS CAUSING ESOPHAGITIS

Ingestion of various products around the house can induce severe esophagitis. The most common products ingested include bleach, laundry detergents, bathroom cleansers, drain cleaners, oven cleaners, and swimming pool products.

Acidic agents taste bad, cause immediate pain, and are rapidly spit or vomited out; because of this, significant ingestions are unusual. They generally cause more injury to the stomach than to the esophagus but can nevertheless cause esophageal damage, although this is rare. Alkaline agents are tasteless and swallowed without consequence initially. The alkalis produce a liquefactive necrosis with intense inflammation of the surrounding tissue. Granular alkalis, like drain cleaners, cause more injury to the mouth, pharynx, and proximal esophagus, while liquid drain openers cause severe injury to the entire esophagus but rarely to the stomach.

Children and infants will present with drooling, dysphagia, or abdominal discomfort. Some will present with airway symptoms only, including stridor, retractions, and nasal flaring. The symptoms can be immediate or delayed for hours, and the lack of symptoms or the lack of significant oral findings do not necessarily correlate with the amount of esophageal or stomach damage. Severe damage can occur without outward signs or symptoms. Observe the child who has no symptoms and no physical findings—and a questionable history of ingestion—for several hours and give clear liquids to see if the child can tolerate them. Those with a definite history should undergo additional tests no matter what their current symptoms or signs are, and they should remain NPO until after endoscopy.

Upper endoscopy is recommended 12–24 hours after the ingestion. Doing the endoscopy before 12 hours may not show the full extent of injury. Burn injuries are divided into 3 classes. 1st degree burns are only superficial and consist of mucosal edema or redness. These lesions heal without scars and are well tolerated. 2nd degree burns extend into the submucosa and muscle layers. These lesions cause scarring and can result in strictures of the esophagus. 3rd degree burns extend through the esophagus and/or stomach and are associated with complete thickness burns and perforations. If you suspect perforation, immediate surgical treatment is required.

Initial management of ingestion of a caustic product is observation. Do not induce emesis, because it will lead

to further esophageal exposure to the agent. Use of neutralizing agents, milk, and large amounts of water are no longer recommended because of the risk of inducing vomiting. NG tubes are also not recommended because they can perforate damaged areas. If the child has developed upper airway disease, you will likely need to use steroids and/or intubate.

Along with observation, some advocate using broad-spectrum antibiotics and IV steroids. Most gastroenterologists consider using this combination in 3rd degree esophageal burns. (But note: Neither antibiotics nor steroids have so far been proven to produce benefit in human studies.) Dilation has been used after stricture formation, and some recommend it after injury, but no studies have proven it is efficacious as a preemptive method.

PILL-INDUCED ESOPHAGITIS

Pill-induced esophagitis is fairly common in children old enough to take pills, especially adolescents who swallow their pills "dry." The most common location for the pill to become stuck is in the mid-esophagus. Tetracycline, doxycycline, aspirin, NSAIDs, and slow-release potassium are the most common pills implicated. The pills adhere to the side of the esophagus, dissolve, and cause local irritation at the site. Symptoms usually begin soon after ingestion, and patients have retrosternal pain and dysphagia. On the Board examination, look for the adolescent who comes in with chest pain and a history of doxycycline for acne. If the diagnosis is not clear-cut, an endoscopy is diagnostic.

Symptoms will usually resolve in 1–3 weeks. Agents to stop acid production may be helpful for severe cases, but generally, no specific therapy is necessary.

INGESTION OF FOREIGN BODIES

Ingestion of foreign bodies is common. (No, we aren't talking about eating French people.) In younger kids, this usually refers to coins. In older kids, it often refers to accidental swallowing of chicken bones or fish bones. There are some psychiatric disorders that appear in childhood/adolescence that may lead to swallowing a variety of weird objects. For the most part, foreign bodies pass without incident. Only about 10–20% require endoscopic removal, and less than 1% require surgical intervention. Perforation anywhere in the GI tract after foreign body ingestion occurs in less than 1%. Once in the stomach, nearly 95% of foreign bodies will pass without problem.

Symptoms, if they occur, are likely due to the foreign body getting stuck just below the cricopharyngeal muscle. Children may present with drooling, choking, or poor feeding. Older children can usually describe retrosternal pain and/or dysphagia. Respiratory symptoms alone can also occur and are usually due to the foreign body pushing against the posterior tracheal wall.

You can diagnose most with standard chest x-ray, because nearly 90% are radiopaque. Coins have a tendency to lie in the coronal plane ("face forward") in the esophagus and the sagittal plane ("on edge") in the trachea. Sometimes contrast material or fluoroscopy is needed to show non-opaque items, such as plastic toys or pieces of toys; however, with a good history of ingestion and physical symptoms, you can usually bypass this option. See Image 14-6, an MRI showing a foreign body in the esophagus (hmm, expensive way to diagnose a foreign body!).

The child or infant who presents with inability to swallow secretions, or who is in respiratory distress, requires immediate evaluation and intervention. Fiberoptic endoscopy is the method of choice to grab and remove objects under direct vision. "Blind" removal with Foley catheters has become popular for removing coins, but you must be careful since some coins have popped over into the trachea in the process of removal, resulting in respiratory distress. Observe for 12–24 hours children who are without respiratory distress and can swallow their own secretions. About 1/3 of these will pass spontaneously. If the item has not passed into the stomach by 12–24 hours, then retrieve it. Items that are smooth and small and cannot be easily grabbed can be pushed into the stomach, so they can pass normally. Remove items longer than 10 cm, because they cannot easily pass the duodenum.

Sharp objects are also usually removed because of the increased risk of morbidity, except for straight pins, which can pass safely. Meat impaction is a special case in adolescents; it may require intervention if the

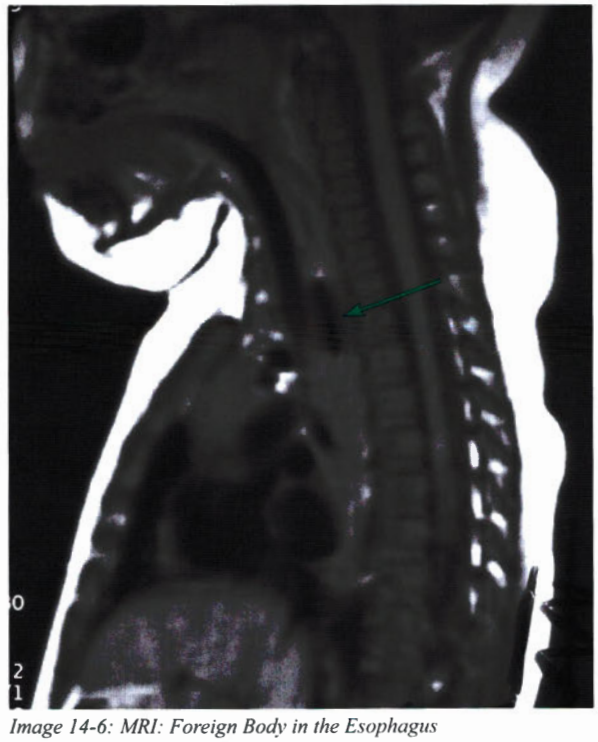


Image 14-6: MRI: Foreign Body in the Esophagus

Quick Quiz

- What are the most common pills that cause pill-induced esophagitis?
- What is the best way to determine if an ingested coin is in the esophagus?
- Spontaneous esophageal perforation is rare but has increased frequency in which 2 disorders?
- How may pyloric stenosis present?
- What type of acid-base disorder is associated with pyloric stenosis?

adolescent is in respiratory distress or cannot swallow secretions. Without these accompanying problems, it will usually pass on its own. The use of meat tenderizer is contraindicated! It can cause hypernatremia and esophageal perforation. Other types of foreign bodies in adolescents and older children often indicate an underlying etiology—often eosinophilic esophagitis.

ESOPHAGEAL PERFORATION

Esophageal perforation is rare in children. However, there are a few things you need to remember for the Board exam. Spontaneous perforation can occur in Ehlers-Danlos and Marfan syndromes. Pain occurs in the chest and upper back, as does subcutaneous emphysema. Fever and hypotension are common. Do not perform endoscopy in these patients! The safest thing to do is to get plain film x-rays, followed by instillation of a small amount of water-soluble contrast material. If the water-soluble contrast material does not show the perforation, you may have to proceed with a barium examination to better outline the abnormality.

Treat surgically, and then begin IV antibiotics and parenteral feeds. You can do enteral feeds by passing the tube past the healing perforation.

STOMACH DISORDERS

PYLORIC STENOSIS

Pyloric stenosis is fairly common, occurring in 1/200 to 1/750 live births. Boys are affected 6 times more often than girls, but don't dismiss a female infant with appropriate symptoms. Firstborn boys were previously thought to be at highest risk, but recent data dispute this. It now appears that it is more closely associated with smaller family size and higher socioeconomic status than with birth order. African-American children are 2–3x more likely to be affected than Caucasian children; Asian-Americans are rarely affected.

Pyloric stenosis usually presents between 3 weeks and 2 months of age with progressive nonbilious projectile vomiting. About 20% have symptoms from birth, but they are not recognized until later. If vomiting is prolonged, hypochloremic alkalosis can develop, along with dehydration. Hypokalemia can also occur.

Studies have shown that the pyloric muscle is normal at birth but hypertrophies soon after and causes obstruction of the pyloric outlet. The etiology is unknown although decreased levels of nitrous oxide are present.

Diagnose with physical examination by observing visible peristalsis and palpating for a mobile pyloric mass known as an "olive." Finding the "olive" means you have made the diagnosis, since it is pathognomonic for pyloric stenosis. It can usually be found in 60–80% of those affected. If you cannot diagnose by physical examination, the next step is either an abdominal ultrasound—which will show a thickened and lengthened pyloric muscle—or the upper GI, which will show elongation and thickening of the pylorus, as well as obstruction of the pyloric outlet by thickened mucosa (Image 14-7). Many advocate beginning with ultrasound due to its safety and high sensitivity.

Aim initial treatment at correcting dehydration and electrolyte abnormalities, particularly hypokalemia and alkalosis, before surgery. Knowing the electrolyte perturbations in this disorder seems to be a Board question favorite. The surgical procedure of choice is the Ramstedt pyloromyotomy, which is curative and has a very low mortality rate (< 0.5%). Full oral feeds can be commenced quickly after surgery. Recurrence rates are less than 1%.

CONGENITAL GASTRIC OUTLET OBSTRUCTION

Congenital gastric outlet obstruction is very rare and occurs in less than 1/100,000 births. Pyloric webs are the most common and are areas of extra gastric mucosa and submucosa that prolapse into the duodenum. Patients

Image 14-7: UGI Showing Blockage at Pyloric Outlet

present with epigastric pain, intermittent nonbilious emesis, or FTT. Perform an endoscopy to define the extent of the lesion.

Some neonates have complete pyloric atresia. They will present with polyhydramnios, nonbilious emesis, and an enlarged, gas-filled stomach—with the rest of the abdomen gasless on plain abdominal x-ray. Pyloric atresia is associated with an autosomal recessive disorder, in which infants have junctional epidermolysis bullosa. In this condition, simple minor skin friction will result in severe vesiculobullous wounds. An upper GI will diagnose the atresia.

Treatment for gastric outlet obstruction consists of a surgical gastroduodenostomy or pyloroplasty with local excision, depending on the extent of the lesion.

CONGENITAL MICROGASTRIA

Congenital microgastria is rare and results in a small tubular stomach associated with a large "megaesophagus" and incomplete gastric rotation. It is also associated with asplenia and situs inversus, as well as limb and cardiac abnormalities. Children with this disorder present with vomiting and FTT. Diagnose with upper GI. Patients may still gradually develop a functional stomach, so it is best to wait on surgery until later in life. Consider surgery if jejunal continuous drip feeds do not produce gastric growth.

EROSIVE AND HEMORRHAGIC GASTROPATHY

Gastritis vs. Gastropathy

The words "gastritis," characterized by the presence of inflammatory cells, and "gastropathy," characterized by the absence of inflammatory cells, are frequently used interchangeably. The words "erosive" and "hemorrhagic" are descriptive of what is seen at the time of endoscopy. In this section, we will discuss the causes of erosive and hemorrhagic gastropathy.

Stress Gastropathy

Stress gastropathy is due to severe physiologic stress, such as occurs with shock, metabolic acidosis, sepsis, burns, and head injury. Initially, the mucosal ischemia occurs in the fundus and proximal body, and later it spreads to the antrum, resulting in a diffuse erosive and hemorrhagic appearance. Prompt control of the underlying disorder improves the gastropathy/gastritis more than any acid-neutralizing therapy.

Traumatic Gastropathy (Prolapse Gastropathy)

Traumatic gastropathy is usually due to forceful retching or vomiting that causes subepithelial hemorrhages in the fundus and proximal body as the proximal stomach is pulled up into the distal esophagus. The hemorrhages tend to resolve quickly, but large amounts of bleeding can occur in a short time period. Mallory-Weiss tears occur in the distal esophagus at the gastroesophageal junction and can extend into the gastric cardia from profound/extended retching, but note that Mallory-Weiss tears are rare in children. NG tubes and foreign bodies can also cause hemorrhages and erosions.

Drug-induced Gastropathy

Aspirin and nonsteroidal antiinflammatory drugs are common causes of minor erosions and hemorrhages in the body and antrum of the stomach. Usually, these have little clinical significance. On occasion, NSAIDs can cause more extensive erosions and hemorrhages, resulting in perforation and excessive bleeding. The injuries result from local, as well as systemic, effects. Alcohol is a well-known cause of gastropathy.

Exercise-induced Gastritis

Exercise, particularly distance running, can produce blood loss with anemia from gastritis or gastropathy. GI symptoms may or may not accompany the anemia. The GI disorder can be erosive or nonerosive.

NONEROSIVE GASTROPATHY

Occurrence

Nonerosive gastropathy is the most common gastritis in children and adults. It usually occurs in the antrum and is a histologic diagnosis, since endoscopy may not show anything visually. Etiologies are varied.

Nonspecific Gastritis

Nonspecific gastritis is fairly common in children, with no identifiable etiology. On biopsy, the inflammation is chronic and superficial, as well as being focal instead of diffuse. The antrum is commonly involved.

Helicobacter pylori Gastritis

Helicobacter pylori is the most common identifiable cause of chronic gastritis in children. An acute infection of *Helicobacter pylori* can result in nausea, vomiting, and halitosis, with a short period of increased acid secretion followed by a marked decrease in acid production. The acute symptoms last only about 1 week. Then, over the next 3–6 months, gastritis resolves and acid secretion returns to normal. Most patients then have a chronic infection with the organism, but in a large majority of individuals, it causes no symptoms.

Diagnosis is confirmed by gastric biopsies showing the gram-negative spiral rods on the surface of the glandular epithelium under the mucous layer. Remember that with nonerosive gastritis, the endoscopic appearance can be normal; therefore, you must biopsy with endoscopy.

QuickQuiz

- What causes stress gastropathy?
- What is the most common, identifiable cause of chronic gastritis in children?
- What usually causes Ménétrièr disease?
- What organism is responsible for most peptic ulcer disease in children?
- Are antibody tests useful in diagnosing active peptic ulcer disease?

Biopsy in children is still considered the gold standard for diagnosis of an acute active infection.

Chronic gastritis due to *H. pylori* can cause atrophic gastritis and intestinal metaplasia in adults. There appears to be no association between early childhood acquisition of *H. pylori* and the development of gastric cancer in adults. However, *H. pylori* is associated with gastric adenocarcinoma and a rare, slow-growing, mucosa-associated lymphoid tumor (MALT) of the stomach, the latter of which is cured with the effective treatment of *H. pylori*.

Crohn Disease

Crohn disease is mentioned briefly here (more in the Intestinal Disorders topic later). It can cause typical aphthous ulcers in the stomach and duodenum, as well as focal, deep gastritis in the antrum of the stomach. On biopsy, look for giant cells and granulomas.

Allergic Gastritis

Allergic gastritis presents with an eosinophilic infiltrate only in the gastric mucosa; it does not go any deeper (this is in contrast to eosinophilic gastritis discussed next). Endoscopy is frequently normal or may show nonspecific swollen folds. It is usually fairly benign. Often, you can identify the allergen and, if exposure to the allergen is prevented, cure is maintained.

Eosinophilic Gastritis

Eosinophilic gastritis can involve all layers of the gastric wall but frequently may lie in only the mucosa, muscle layers, or subserosa. It is less common than allergic gastritis and is usually much more severe. Biopsy may not be helpful; remember that only the deeper layers may be involved, and eosinophilic gastritis would not be picked up by the standard mucosal biopsy.

Ménétrièr Disease

Ménétrièr disease is a protein-losing gastropathy that results in hypoproteinemia. On endoscopy, the stomach fundus and body are folded and swollen. Typically, it will present as peripheral edema with nausea and vomiting, frequently after an apparent viral illness. Biopsy will show long, tortuous pits and a swollen lamina propria. You will also notice increased numbers of eosinophils and round cells in the lamina propria. It almost always is due to CMV infection. It resolves over several weeks to months in children, but in adults it is a chronic, unremitting disease.

PEPTIC ULCER DISEASE (PUD)

Overview

Peptic ulcer disease is very rare in children and is nearly always related to *H. pylori*; however, many children have *H. pylori* infection, while very few develop peptic ulcer disease. Only 20% of children with peptic ulcer disease have what is known as "idiopathic" disease (i.e., not due to *H. pylori*). Since these disorders are rare, assume they are secondary to other causes.

H. pylori is another sticky issue. Why? Because a large number of children have *H. pylori*, and a large number of children have complaints of abdominal pain, but very few children's abdominal pains are due to *H. pylori*. Thus, the presence of *H. pylori* alone is not helpful as a diagnostic indicator. Therefore, you must individualize the use of tests to look for *H. pylori* based on specific findings in each patient.

Do not use antibody tests that use blood, serum, or saliva from children. Remember that a positive antibody test may indicate past exposure and not necessarily active, ongoing infection. Urea breath tests (^{13}C or ^{14}C) are acceptable in children, but remember that the presence of *H. pylori* does not indicate pathology or rule out alternative diagnoses. Urea breath tests are best used after therapy for peptic ulcer disease to determine if *H. pylori* has been eradicated. Endoscopy is the test for children with upper GI bleeding, recurrent vomiting, or persistent, undiagnosed abdominal pain. An upper GI series is unacceptable in children for diagnosis of peptic ulcer disease.

Treatment of PUD

Treatment of peptic ulcer disease is multifactorial. Pharmaceutical agents to reduce acid secretion are helpful to treat symptoms, as well as to heal erosions and ulcers more quickly. Ranitidine is commonly used, as are proton pump inhibitors (PPIs). Antacids are not recommended for most cases.

However, the key in *H. pylori*-induced disease is to eradicate the *H. pylori* infection. Additionally, in the presence of a positive *H. pylori* test, anti-*H. pylori* therapy is given only when peptic ulcer disease is proven, or in MALT lymphoma. In children, do not treat "*H. pylori*" colonization indiscriminately.

You can treat duodenal ulcer with 2 weeks of a PPI, clarithromycin, and either amoxicillin or metronidazole. All 3 drugs are given in divided doses, twice a day. Ulcers with complications (bleeding, perforation, or penetration) will commonly relapse, so it is appropriate to perform a follow-up endoscopy to confirm healing and eradication of *H. pylori*. For "uncomplicated" ulcers, most suggest symptom resolution and a follow-up urea breath test for *H. pylori* eradication. Do not do follow-up urea breath tests until at least 4–6 weeks after acid suppression therapy has ended. No dietary modification is recommended.

Surgery is rarely indicated but may be required if there has been perforation of the stomach or duodenum; active bleeding cannot be controlled; gastric outlet or duodenal obstruction has occurred; or medical therapy has failed, as in hypersecretory syndromes (see next).

Acid Hypersecretory Diseases

Note

A few acid hypersecretory diseases also exist. Note that for all of the hypersecretory diseases discussed next, about 10% will present with diarrhea and no ulcers. Mucosal resistance (likely due to genetic factors) prevents ulcer formation in these individuals.

Zollinger-Ellison Syndrome

Zollinger-Ellison syndrome (ZE syndrome) is rare in children. It produces markedly excessive stomach acid due to a gastrin-secreting tumor (gastrinoma) of the pancreas, duodenum, or other, less common site. Multiple ulcers are common and frequently involve unusual sites for ulcers, such as the esophagus, stomach, or jejunum. The majority of gastrinomas are malignant but slow-growing tumors. Perform surgical resection of the tumors if possible, but metastases to the lymph nodes and liver accompany poor prognoses. Gastrinomas are strongly associated with MEN-I. About 25% of people with gastrinoma have MEN-I (so evaluate them for hyperparathyroidism and adrenal tumors as well!), and 50% of those with MEN-I have gastrinoma. A very similar rare syndrome is antral G-cell hyperplasia.

Systemic Mastocytosis

Systemic mastocytosis is also associated with acid hypersecretion. It is a disease wherein mast cells accumulate in the skin, marrow, liver, spleen, and GI tract. Hyperparathyroidism is also noted with this disorder.

INTESTINAL DISORDERS

MALROTATIONS OF THE INTESTINE

Malrotation of the intestine can present anytime in childhood and may be due to nonrotation, incomplete rotation, paraduodenal hernia, or reverse rotation. Malrotation occurs in about 1/6,000 births. Gastroschisis and omphalocele always have malrotation as well (see below).

Nonrotation is the most common malrotation abnormality and presents with the cecum on the left and the small intestine to the right of the superior mesenteric artery. This results in a short mesentery and relatively little fixation of the bowel. The duodenum is small and fuses with the colon, using a common mesentery around the superior mesenteric artery.

Infants with malrotation classically present in the 1st month of life (90% present within the 1st year), with an acute process of bilious emesis due to an acute midgut volvulus. These infants present with abdominal distention and irritability, and, if the bowel strangulates, septic shock is likely. As the bowel necrosis worsens, the infant may develop hematemesis, melena, or both. Rapid surgical correction is mandatory; without it, the infant will die or develop intestinal ischemia that results in short gut syndrome. Occasionally, a child will be asymptomatic until later childhood or even until adulthood.

In an infant who has bilious vomiting with findings of malrotation and volvulus, perform an upper GI series for diagnosis. The upper GI series will demonstrate the classic "bird's beak" of the 2nd or 3rd portion of the duodenum, where the gut is twisted (Image 14-8). If the duodenum is partially obstructed, you may see a "corkscrew" pattern. For the older child with intermittent symptoms, the upper GI series can identify an abnormal location of the duodenojejunal junction (the ligament of Treitz). Normally, the ligament of Treitz is to the left of the spine at the level of the gastric antrum and is fixed to the posterior body wall. In malrotation, the ligament of Treitz is on the right side of the spine and is inferior to the duodenal bulb. Thus, in malrotation, contrast from the upper GI will fill the jejunal loops on the right side of the abdomen.

After emergent management of the initial shock and cardiovascular compromise, immediately perform a Ladd procedure. The Ladd procedure consists of opening the

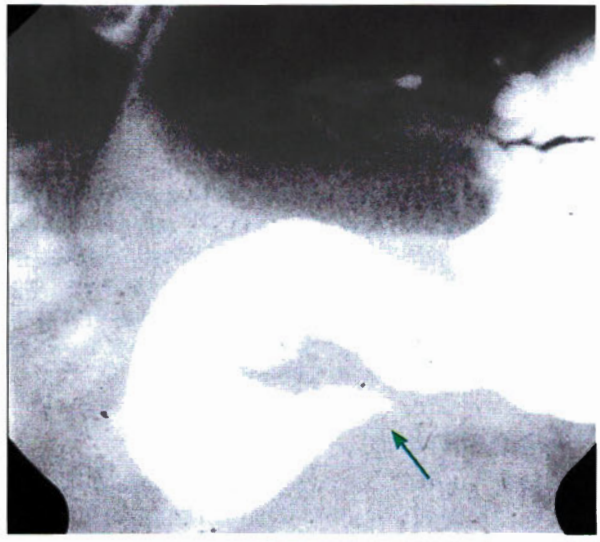


Image 14-8: Volvulus with "Bird's Beak" Sign

Quick Quiz

- What is Zollinger-Ellison syndrome?
- At what age do infants with malrotation classically present?
- What does an upper GI series show in an infant with malrotation?
- At what age does intussusception usually occur?
- What is the classic triad of presentation for intussusception?
- What should the term "currant jelly" make you think of?
- What is the diagnostic procedure of choice for intussusception?
- What do abdominal plain x-rays show in duodenal atresia?
- Which is associated with other congenital anomalies—jejunoileal or duodenal atresia?

abdominal wall and taking out the intestines to inspect the mesenteric root. If the surgeon finds volvulus, they will untwist it and inspect the bowel for viability. During surgery, they will resect nonviable or necrotic areas, and perform enterostomies. If "questionable" areas of bowel are found, these are generally left in place; then after 12–36 hours, a "2nd look" surgery is performed to assess viability.

If a child is diagnosed with a malrotation but is asymptomatic, most recommend an elective Ladd procedure as quickly as possible.

INTUSSUSCEPTION

Intussusception occurs when one part of the intestine "telescopes" into the lumen of the adjoining bowel. With this folding, mesentery is dragged into the process, which can cause venous obstruction, swelling, and/or edema of the bowel wall. Eventually, the edema can cause arterial obstruction, ischemia, and perforation. Intussusception usually occurs between 2 months and 5 years of age, with a peak incidence between 4 and 10 months. Almost all are idiopathic. Most originate near the ileocecal junction, and many believe these are due to a virus-induced swelling of Peyer patches. The initial rotavirus vaccine (now replaced by a newer vaccine) was associated with an increased incidence of intussusception, which led to removal of the original rotavirus vaccine from the market.

Intussusception presents as a triad of abdominal pain, vomiting, and bloody stools. An infant with intussusception will awaken with crying and have flexion of the knees and hips, demonstrating the severe abdominal pain. Frequently, the pain subsides, and the child appears comfortable. A normal bowel movement is common with the pain, but future bowel movements will be "currant jelly" in appearance and may occur hours or days after the abdominal pain. Eventually, the pain episodes increase in severity and frequency. Examination between episodes will show a soft abdomen, and, in a majority during an episode, you may be able to palpate a sausage-shaped mass in the right upper quadrant or mid-upper abdomen.

Plain abdominal x-rays may show a soft tissue mass displacing loops of bowel. An air-contrast enema is the diagnostic (and therapeutic) procedure of choice. Nearly 90% may be reduced with the procedure. Peritonitis is an absolute contraindication—and bowel obstruction is a relative contraindication—for an air-contrast enema. Recurrence rates are between 3 and 10%, and most recommend admission for 24-hour observation. If the air-contrast enema is unsuccessful, quickly perform a laparotomy.

CONGENITAL INTESTINAL ATRESIAS

Occurrence

Atresias of the gut happen in about 1/5,000 births, with most occurring in the duodenum or other areas of the small intestines. Type I atresias consist of a normal muscular wall with an intraluminal membranous web. Type I atresias may or may not have a small fenestration. Type II atresias have a fibrous cord that connects the 2 ends of the separated bowels. Type III atresias have 2 blind-ending pouches of bowel with a wedge-shaped mesenteric defect. Type IV atresias have multiple segments of atretic bowel and give a "string of sausages" appearance.

Duodenal Atresia

Duodenal atresia accounts for over 50% of the intestinal atresias. Duodenal atresia is associated with multiple anomalies, including cardiac, GU, anorectal, and esophageal. About 50% will be in premature neonates. 40% of patients with duodenal atresia will have trisomy 21. If there is complete obstruction, the patient presents with polyhydramnios and a dilated stomach on prenatal ultrasound. A majority will have their obstruction distal to the ampulla of Vater; so they also will have bilious vomiting. Abdominal plain x-rays will show the classic "double bubble" (Image 14-9). This is diagnostic if the rest of the bowel is airless. If there is distal gas, you can confirm with an upper GI. Surgery is necessary, and most of the complications occur due to the associated cardiac abnormalities.

Jejunoileal Atresia

Jejunoileal atresia is different from duodenal atresia in that jejunoileal atresia is not associated with other congenital anomalies. Prenatal diagnosis is possible


Image 14-9: Duodenal Atresia

with maternal ultrasound. Postnatally, those affected present with abdominal distention and bilious emesis. They may or may not have meconium stools. Abdominal x-rays show multiple, dilated loops of bowel with air-fluid levels. Diagnosis is best made with an upper GI or lower GI, and it must be differentiated from meconium ileus, which is seen with cystic fibrosis. Surgery is necessary, with the goal of salvaging as much small bowel as possible.

Colonic Atresia

Colonic atresia is the rarest of the intestinal atresias. If the colon is the only segment involved, patients present with distal bowel obstruction, abdominal distention, bilious emesis, and failure to pass meconium. Confirm diagnosis with a contrast enema, which will show a distal microcolon and the point of obstruction. Surgical reanastomosis is the treatment of choice.

MECKEL DIVERTICULUM

Meckel diverticulum occurs when the vitelline duct fails to be obliterated. The vitelline duct connects the yolk sac to the primitive gut in the developing fetus and usually is obliterated between the 5th and 9th weeks of gestation. The Meckel diverticulum is usually not attached to the umbilicus. Meckel diverticulum is a "true" diverticulum containing all 3 tissue layers. The blood supply comes off of the right vitelline branch of the superior mesenteric artery. A unique characteristic of Meckel diverticulum is that the blood supply terminates on the antimesenteric rather than the mesenteric side of the bowel.

Additionally, ectopic tissue is common, with 80% being of gastric origin and 5% of pancreatic origin.

For Meckel diverticulum, you must know the "rule of 2s":

- Occurs in 2% of the population
- Located within 2 feet of the ileocecal junction
- Measures 2 inches in length
- Measures 2 centimeters in diameter
- 2:1 male-female ratio
- Usually symptomatic before 2 years of age (if and when symptoms are actually present)

For the most part, Meckel diverticulum is clinically asymptomatic. When found, it is an incidental finding discovered during some other surgery. The lifetime risk of complication from Meckel diverticulum is 4%. If symptoms are going to occur, they will generally occur before the age of 2 years. The main symptoms are due to gastrointestinal bleeding from ectopic gastric mucosa. In fact, Meckel diverticulum is the most common cause of serious lower GI bleeding in children.

Meckel diverticulum is associated with other congenital anomalies, including esophageal atresia (6x risk), imperforate anus (5x risk), neurologic (3x risk), and cardiovascular (2x risk). Patients with Crohn disease have 3x increased risk of Meckel diverticulum.

Painless rectal bleeding is the most common presenting symptom. Occasionally, colicky abdominal pain will accompany the bleeding. The color of the blood can be bright red or maroon and has been described on occasion to resemble intussusception with "currant jelly" character. Transfusions are often required because of the large amount of bleeding that occurs. Bleeding tends to stop and start spontaneously.

Diagnosis is difficult. Most prefer a technetium ^{99m}pertechnetate scan (also called the Meckel scan). This scan works because a majority of bleeding Meckel diverticulum will have ectopic gastric mucosa. The ^{99m}pertechnetate will concentrate in the parietal cells of gastric mucosa and the bladder. A positive scan is indicated when finding isotope uptake outside of the stomach and bladder. Histamine H_2 blockers can enhance the accuracy of the scan. If suspicion is high and the initial scan is negative, repeat the scan. The sensitivity of the Meckel scan is 85% (Remember: This means that of 100 people with known Meckel diverticulum, the test will pick up 85; thus, 15 will be "missed" by the scan); the specificity is 95% (this means that of 100 people without a Meckel diverticulum, the test will be negative 95% of the time; 5% will have a false-positive test). Finally, if repeat scans are negative and you are still convinced it is probably Meckel diverticulum, perform a laparoscopy.

Meckel diverticulum requires surgical intervention. Fluid and blood are usually required before surgery if the inciting event is severe. If Meckel diverticulum is found as an incidental finding during an abdominal surgery in a young child, most pediatric surgeons would resect it. For older children or adults, resection is controversial because the risk of bleed if left alone is much lower in these older groups.

Quick Quiz

- What is the "rule of 2s" in Meckel diverticulum?
- What is the best test with which to diagnose Meckel diverticulum?
- What is the common carbohydrate metabolism deficiency in the United States that starts after the age of 2 years?
- What is the best test to diagnose lactase deficiency?

INTESTINAL DUPLICATIONS

Intestinal duplications are rare and may occur anywhere from the mouth to the anus, but the most common location is in the ileum.

3 characteristics are required by definition:

1) Each is contiguous and strongly adherent to some part of the GI tract.
2) The duplication has a 2-layered muscular coat.
3) The duplication is lined with mucosa or epithelium similar to that of the stomach, small intestine, or colon.

Intestinal duplications are located on the mesenteric instead of the antimesenteric side of the bowel and share a common blood supply with its adjacent bowel. This differs from Meckel diverticulum, which occurs on the antimesenteric side of the bowel. About 1/4 will have ectopic mucosa, which is usually gastric but occasionally pancreatic in character. Remember that having ectopic gastric mucosa predisposes to bleeding and peptic ulceration.

Complications from intestinal duplications can include obstruction, intussusception, bleeding, pain, and perforation. It is common for them to present with abdominal pain and frequent vomiting. You can confirm diagnosis with exploratory laparotomy for the symptoms/complications. See Image 14-10, an ultrasound image showing intestinal duplication.

Gastric duplications, another type of intestinal duplication, occur most commonly in girls under the age of 1. They are much rarer than the ileal location and make up only about 5% of intestinal duplications. Gastric duplications are usually cystic and are located on the greater curvature of the stomach. They do not communicate with the stomach lumen. Major complications include bleeding and ulcerations, since they contain gastric mucosa and secrete acid. Treat by resecting the duplication.

Colonic and rectal duplications, additional types of intestinal duplications, are very rare and are associated with GU malformations. Rectal duplications may be confused with rectal prolapse, hemorrhoids, or fistulas.

MECONIUM ILEUS

Meconium ileus and meconium plug syndrome are discussed in The Fetus & Newborn section.

CARBOHYDRATE MALABSORPTION

Lactase Deficiency (Lactose Intolerance)

Lactase deficiency is a common disorder in the U.S. after the age of 2 years. Lactase is normally found on the brush border near the tips of the intestinal villi, and it cleaves lactose, allowing absorption of its parts, glucose and galactose. Primary adult-type hypolactasia (known as adult-onset lactase deficiency) is the most common genetic cause of carbohydrate malabsorption. It is due to a post-weaning decline in intestinal lactase-specific activity. (Infants are universally able to ingest lactose-containing breast milk and other milk products.) In individuals with this genetic disorder, the lactose gene (located on chromosome 2q21) "down-regulates" and produces a much lower level of lactase. This can occur as early as the second year of life and may or may not persist into adulthood. Most of the world's populations become "lactase deficient," except for Caucasian populations of northern and central European descent. Symptoms of diarrhea and recurrent abdominal pain can occur in those with low levels of lactase who consume a large amount of lactose-containing foods.

Measurement of stool-reducing sugars (using Clinitest®) and fecal pH can be useful screening methods. However, these tests usually require a liquid, fresh stool obtained after the patient has consumed the offending carbohydrate.

The breath hydrogen test is the most common reliable diagnostic test. When carbohydrate is malabsorbed, bacteria in the colon produce hydrogen gas, which is then absorbed across the colon mucosa into the

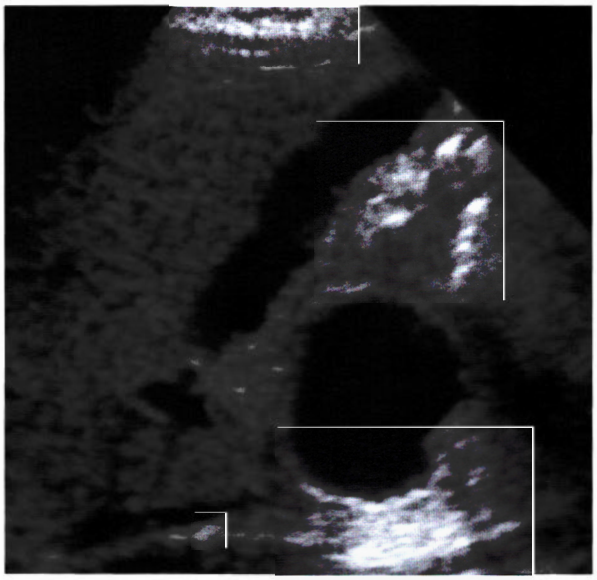


Image 14-10: Intestinal Duplication

bloodstream, transported to the lungs, and expired. In the breath hydrogen test, breath is sampled sequentially after the patient is given a test carbohydrate substance. A rise of more than 10–20 ppm in expired hydrogen indicates that the carbohydrate is not being digested, and then absorbed, properly. If the rise is too early, this usually indicates bacterial overgrowth. A child on antibiotics may produce a false-negative test, since the bacteria needed for hydrogen production are missed due to the presence of the antibiotics.

Endoscopic biopsy with measurement of mucosal enzyme activity is the gold standard study for disaccharide activity but is rarely done today because of the invasiveness and expense.

Lactase deficiency in infancy is usually transient and due to a secondary cause (see below), and it responds to temporary alteration in diet. Older children and adults with lactase deficiency can generally do well by avoiding large quantities of lactose-containing foods and limiting themselves to small amounts of lactose, such as is in cheese. Those wanting to increase their lactose tolerance can use microbial-derived lactase enzyme (Lactase®) with meals.

There also is a "congenital" lactase deficiency that presents at birth and is very rare except in Finland. It is autosomal recessive and resolves with removal of lactose from the diet.

Fructose and Sorbitol Malabsorption

Fructose and sorbitol are used extensively in commercial food products. Fructose is used as a sweetener, especially as high-fructose corn syrup in soft drinks. Sorbitol is a poorly absorbed sugar best known for its use in "diet" foods.

Both fructose and sorbitol may be malabsorbed if consumed in quantities that exceed the ability of the intestine to break down and absorb these sugars. The transport carrier protein is GLUT5, located on the apical membrane of the enterocyte, and it can be overwhelmed by excessive quantities of these sugars. Fructose malabsorption is associated with diarrhea, abdominal pain, and distention. Fruit juices with high fructose-to-glucose ratios and those with sorbitol (apple, pear) may cause nonspecific diarrhea and recurrent abdominal pain.

Table 14-4: Congenital Transport Defects

Name	Defect	Symptom
Abetalipoproteinemia	Apo B	Steatorrhea, FTT
Chylomicron retention	Chylomicron exocytosis	Steatorrhea, FTT
Congenital chloride diarrhea	Cl^-/HCO_3 exchanger	Low pH diarrhea, alkalosis
Congenital sodium diarrhea	Na^+/H^+ exchanger	High pH diarrhea, acidosis

Sucrase-isomaltase Deficiency

Sucrase-isomaltase deficiency is an autosomal recessive disorder that first appears when sucrose-containing formula or fruits are introduced to the older infant. It occurs in about 5/1,000 in the U.S.; but in some Canadian populations, it has been reported to occur as commonly as 1/10. These children have low levels of sucrase and maltase and cannot digest starches easily. They can present with mild-to-severe diarrhea and abdominal pain. Sacrosidase, an enzyme derived from *Saccharomyces cerevisiae*, is a potent sucrase and can be taken with meals to overcome sucrase deficiency.

Secondary Carbohydrate Malabsorption

Secondary carbohydrate malabsorption is very common in diseases that cause intestinal mucosal damage or atrophy. Rotavirus is the most common infectious agent. *Giardia* infection and HIV also cause carbohydrate malabsorption. Conditions of bacterial overgrowth can lead to impaired monosaccharide transport. Secondary carbohydrate malabsorption can also affect infants with short gut syndrome who don't have enough surface area to complete carbohydrate digestion. Finally, children with cystic fibrosis or other causes of pancreatic insufficiency cannot absorb starches adequately, due to reduced or absent amylase.

CONGENITAL TRANSPORT DEFECTS

For the Boards

Congenital transport defects are rare. For the Board exam, you generally just have to know the "syndrome" and the "defect." But a few require further discussion. (See Table 14-4 and Table 14-5.)

Abetalipoproteinemia and Other Disorders of Fat Transport

Abetalipoproteinemia is an autosomal recessive disorder. With this disorder, there is congenital absence of apo B, which results in an inability to synthesize chylomicrons. Patients present with very malodorous

Table 14-5: Congenital Transport Defects

Name	Transport Defect and Result
Hartnup disease	Free, neutral amino acids; pellagra-like
Blue diaper syndrome	Tryptophan
Lowe syndrome	Lysine and arginine; MR, cataracts, rickets
Acrodermatitis enteropathica	Zinc; rash, diarrhea, FTT

Quick Quiz

- What does the absence of apo B result in?
- What is Hartnup disease?
- How do children with abnormal zinc absorption present?

steatorrhea and FTT. Fat-soluble vitamins cannot be absorbed, eventually leading to development of night blindness, sensory ataxia, and nystagmus. Retinitis pigmentosa is present. Acanthocytosis occurs in the blood due to abnormal membrane lipids in the blood cells. Serum cholesterol is extremely low, and triglyceride levels are just barely detectable. You can confirm by observing an absence of β-lipoprotein in the blood. Treat by limiting dietary intake of long-chain fatty acids and giving medium-chained triglycerides. Supplement with vitamins E, A, and K. An autosomal dominant disease known as hypobetalipoproteinemia presents similarly with deficiency of apo B.

Chylomicron retention disease (Anderson disease) is an autosomal recessive disorder that occurs due to defective exocytosis of chylomicrons. It presents mainly with diarrhea, steatorrhea, and low serum cholesterol without the severe acanthocytosis, retinitis pigmentosa, and neurologic abnormalities seen with the abeta- and hypobetalipoproteinemias.

Amino Acid Transport Defects

Amino acid transport defects are rare and can involve the small intestine enterocyte, as well as the proximal renal tubule. Clinically, these can be asymptomatic to severe.

Hartnup disease is due to a defect in transport of free neutral amino acids. It results in a deficiency of nicotinamide synthesized from tryptophan and leads to pellagra-type findings. Blue diaper syndrome is due to isolated malabsorption of tryptophan. Lowe syndrome is due to malabsorption of lysine and arginine and presents with mental retardation, cataracts, hypotonia, and vitamin D–resistant rickets. You can detect all of these with analysis of urine amino acids (see the Metabolic Disorders section for more).

Congenital Electrolyte Diarrhea

Congenital electrolyte diarrhea can be a chloride defect, a sodium defect, or a zinc defect.

For congenital chloride diarrhea, the defect involves the Cl^-/HCO_3^- exchange transport system in the ileum and colon. This results in watery diarrhea with a high chloride and low bicarbonate and pH. You can recognize these infants *in utero* with the presence of polyhydramnios due to the excessive diarrhea. Dehydration is common, as is metabolic alkalosis and hypochloremia at birth and in the newborn period. The diarrhea resolves over time, by 3–4 years of age. Congenital sodium diarrhea presents very similarly but has stool sodium concentrations that are higher than the chloride, and the stool is alkaline instead of acidic. This is a result of a defect in the Na^+/H^+ exchange transport. This results in a metabolic acidosis instead of a metabolic alkalosis.

Abnormal zinc absorption results in acrodermatitis enteropathica, which is an autosomal recessive disease found on chromosome 8q24.3. Zinc is not adequately absorbed and results in bullous and pustular dermatitis. Additionally, alopecia, blepharitis, conjunctivitis, diarrhea, and FTT are common. Breast milk contains the missing zinc-binding factor, so symptoms won't appear in a breastfed infant until 2–3 weeks after weaning has occurred. Deficiency will develop 1–2 months after birth in a non-breastfed infant. You can confirm diagnosis by the above classic clinical findings and by demonstrating a zinc concentration below 50 µg/dL. Treat with oral elemental zinc 35–100 mg daily for life.

SHORT GUT SYNDROME

Short gut syndrome is a malabsorption disorder caused by shortened intestinal length, due to congenital anomalies of the gut or to resection of the small intestine. Common causes include necrotizing enterocolitis, volvulus, malrotation, multiple atresias, and gastroschisis. There also exists a congenital short bowel syndrome, but it is not common. The malabsorption is because of a lack of mucosal absorptive surface due to the anomaly or resection. Other contributing factors may be bile acid deficiency and bacterial overgrowth syndromes.

Just how much bowel is required for normal good health isn't clear. We do know that most infants with at least 38 cm of small intestine survive, and those with less than 15 cm die or require small intestinal transplantation. Normally, infants have 200–300 cm of small intestine. This lengthens to 600–800 cm in adulthood. Recently, there have been reports of survival with shorter bowel lengths, so it appears that a more important factor may be the functional capacity of the remaining bowel.

If the defect is in the duodenum, expect decreased iron, folate, and calcium absorption, which results in anemia and osteopenia. If the defect is in the jejunum, there are generally no specific ill effects except the loss of absorptive surface area. If the defect is in the ileum, though, the result is severe, with large fluid and electrolyte losses. Remember that the ileum is responsible for absorption of 2 specific items: 1) bile salts, and 2) vitamin B_{12}. Inability to absorb bile salts results in fat malabsorption, and vitamin B_{12} deficiency results in macrocytic anemia.

If the short gut is due to surgery, adaptive measures in the remaining small intestine usually kick in and eventually result in improved absorption. Again, this depends largely on how much and what part of the small intestine remains,

as well as how much functionality of the mucosal area is left. If symptoms do not improve, or TPN is required for lifelong survival, consider an intestinal transplant.

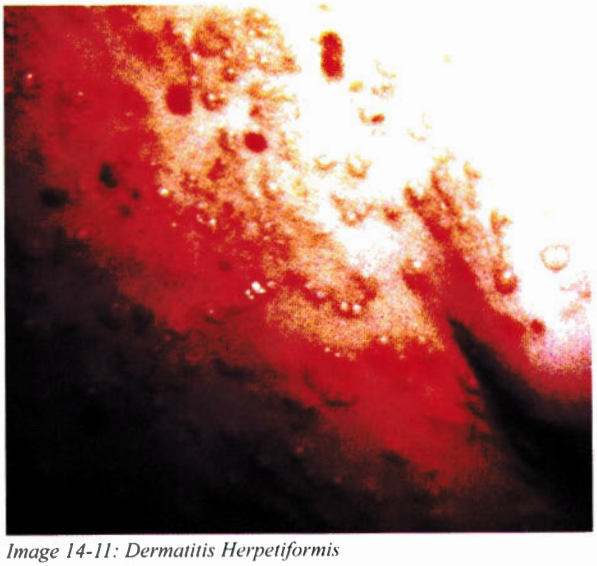
CELIAC DISEASE

Celiac disease occurs in genetically predisposed children and adults after exposure to specific dietary proteins, and it results in immunological cross-reaction–mediated small intestine mucosal damage. Gluten from wheat products and similar proteins found in rye and barley can induce the immune reaction to human transglutaminase and the resulting mucosal damage. Preventing exposure to these products will result in cure and remission. It can be common in certain races and cultures, with 1/250 affected in some European countries. A similar rate of incidence was noted in Denver, Colorado.

HLA typing shows only 2 HLA types are associated with celiac disease, DQ2 and DQ8. Penetrance is variable, and people with known genetic markers for celiac disease do not necessarily develop it. The immune response initially is seen in the duodenum but eventually spreads to the jejunum and ileum. The mucosal lesions are characterized by increased numbers of lymphocytes, plasma cells, and macrophages in the lamina propria and by increased numbers of intraepithelial lymphocytes.

Clinically, patients can present with a variety of symptoms. The "classic" GI form of the disease presents in the child < 2 years of age with symptoms that include malabsorptive diarrhea, poor weight gain, abdominal distension, and proximal muscle wasting. If the malabsorption is significant, look out on the Boards for the child with resulting vitamin D deficiency and hypocalcemia that presents with seizures and hypocalcemic tetany.

But in the late 20th and early 21st century, it has become progressively more obvious that there are multiple presentations of this disease at a variety of ages, and not all of them are gastrointestinal. Celiac disease today (for reasons that are unclear) often presents with symptoms in the adolescent or adult rather than the young child. But the mucosal damage that is occurring precedes the symptoms for many years. When symptoms do occur in this older age group, they can still be gastrointestinal in nature, with diarrhea, abdominal pain, distention, and bloating. More frequently, you may observe extragastrointestinal symptoms, with delayed puberty and poor growth.



Courtesy of CDC

Image 14-11: Dermatitis Herpetiformis

Dermatitis herpetiformis—presenting as extremely itchy, bullous lesions on the extensor surfaces of the arms, legs, trunk, and scalp—can occur with or without GI symptoms (Image 14-11).

Autoimmune disorders are common with celiac disease and can include Type 1 DM, autoimmune thyroid disease, Sjögren syndrome, collagen vascular disease, liver disease, and IgA glomerulonephritis. It is so common in children with Type 1 DM and selective IgA deficiency that they should be screened for celiac disease. Additionally, celiac disease is 50x more common in children with Down syndrome.

Laboratory screening is readily available. The most common tests are antibody tests. Most recommend checking for IgG antigliadin antibodies, IgA antigliadin antibodies, IgA anti-endomysium antibodies, and IgA antibody to tissue transglutaminase. The older antigliadin antibodies have poor sensitivity and specificity, but are included since the IgG antibody will occasionally pick up the patients that are IgA deficient. However, because the antigliadin is also responsible for some false positives, it has been recommended by some expert panels that it be dropped as a screen. If the serologic testing is positive (or if clinical suspicion is high in the face of negative serologic testing), confirm the diagnosis with small intestinal biopsy.

There are 2 mandatory requirements for diagnosis:

1) Characteristic histology on small intestinal biopsy
2) Complete clinical remission with a gluten-free diet

It is very rare now to undertake the old diagnostic protocol of classic histology that responds to dietary elimination of gluten and relapse of histologic disease with rechallenge. Notice that this required 3 endoscopies for biopsy!

Treat with dietary exclusion of wheat, barley, and rye—this is really very difficult to do, but an increasing number of products are becoming available to these patients. You can monitor for low or zero anti-endomysium or anti-tissue transglutaminase antibody levels to determine if gluten and other products are being effectively excluded from the diet.

QuickQuiz

- What dietary protein induces celiac disease?
- How does the classic GI form of celiac disease present in children under the age of 2 years?
- Children with Type I DM and selective IgA deficiency should be screened for what disease?
- What is congenital microvillus inclusion disease?
- What organism causes Whipple disease?
- What part of the GI system does ulcerative colitis affect?
- How do you diagnose ulcerative colitis?

CONGENITAL MICROVILLUS INCLUSION DISEASE

Congenital microvillus inclusion disease (Davidson disease, familial protracted diarrhea, microvillus atrophy) is an autosomal recessive disorder and the most common cause of congenital diarrhea. If the villi of the small intestine are examined under a microscope, they will show diffuse thinning of the mucosa without crypt hypertrophy or an inflammatory cell reaction. The characteristic electron microscopy finding is the presence of microvilli within involutions of the apical membrane.

Infants present early in life with severe watery diarrhea and FTT. Fecal water losses can exceed 800 mL/kg/day. The excessive water loss continues even when nothing is given orally. Tests for intestinal absorption are all abnormal, including fecal fat, and infants present with a marked secretory diarrhea with very high stool electrolytes. Death rates are above 80%. No treatment is effective. If children do survive, they are maintained on parenteral nutrition for life or else require small intestinal transplantation.

TROPICAL SPRUE

Tropical sprue is mainly seen in long-term visitors (at least 3 months) or inhabitants of endemic regions of the tropics, which include India, parts of Asia, the Philippines, areas of South America, Central America, parts of the Caribbean, and areas of central and southern Africa. Sprue can occur in children but is more common in adults. Many believe it is infectious, but so far no pathogen has been found. Malabsorption of sugars, fats, folate, and vitamins A and B_{12} occurs. Early in the disease, fatigue, diarrhea, and anorexia are common. The diarrhea is accompanied by abdominal cramps and flatulence. Nutritional deficiencies eventually occur and present as night blindness, cheilosis, glossitis, stomatitis, and hyperkeratosis. Edema and muscle wasting occur in the final stages of the disease. It can take 6 months to several years for the final stages to occur. Treat with oral broad-spectrum antibiotics and nutritional supplements, including folate and vitamins A and B_{12}.

WHIPPLE DISEASE

Whipple disease is very rare in children and presents as a multisystem disorder resulting in severe malabsorption. You may frequently note arthritis, polyserositis, and CNS symptoms. Fever is also prominent. The etiology is a gram-positive actinomycete called *Tropheryma whippelii*. The hallmark is finding PAS-positive granules in the lamina propria. You must treat with antibiotics for 6 months or longer for cure.

ULCERATIVE COLITIS

Overview

Ulcerative colitis (UC) and Crohn disease make up the inflammatory bowel diseases. UC occurs less commonly than Crohn disease, and 12 years is its mean age of diagnosis. In UC, the inflammation is restricted to the colon and does not involve the small intestine (I remember this with a simple mnemonic: UC = Unanimously Colon). UC involves only the mucosa—mucosa that is continuous without skip lesions. The mucosa is typically worse the lower the area in the colon. The rectum is also involved in most untreated cases. See Table 14-6 for comparisons of UC and Crohn disease.

Presentation of UC

Patients present with fever, abdominal pain, and bloody diarrhea; however, at onset, most patients have only nonbloody diarrhea. Generally, the more severe the symptoms, the more severe the colonic involvement. Fever and arthralgias/arthritis are the most common extraintestinal findings. The arthritis is migratory, asymmetric, and mainly involves the hip and/or knee. Clubbing is common in prolonged disease. Ankylosing spondylitis, erythema nodosum (Image 14-12), and pyoderma gangrenosum (Image 14-13) can all occur. Primary sclerosing cholangitis occurs in about 3% of patients and sometimes presents before the colonic disease. There is also increased prevalence of deep vein thrombosis and pulmonary emboli.

Diagnosis of UC

You can make a diagnosis with endoscopy and characteristic biopsies. Antineutrophil cytoplasmic antibody staining with perinuclear highlighting (p-ANCA) is found in 60% of patients with UC. However, p-ANCA is not specific for UC, since 10–15% of patients with Crohn's, particularly those who present with UC-like disease, also have a positive p-ANCA. Most pediatricians do not routinely perform barium enema. Plain films can be done in an acutely ill child. With severe

Table 14-6: Comparison of Ulcerative Colitis and Crohn Disease

	Ulcerative Colitis	Crohn Disease
Bowel involvement	Colon and rectum only	Anywhere from mouth to anus
Pattern of lesions	Continuous	Skip lesions
Involvement of tissue	Mucosal only	Transmural disease
Granulomas likely	No	Yes
p-ANCA	60%	10–15% (mainly UC-like presentations)
Anti-*Saccharomyces* antibodies	5%	60%
Weight loss	Some	Severe
Gross rectal bleeding	Common	Less common
X-ray findings	Superficial disease, loss of haustrations, thumbprinting	Skip areas, string signs
Perianal lesions	None	Common
Aphthous mouth ulcers	Rare	Common
Growth failure	Rare	Common

colitis, you will see thickening of the colonic wall ("thumbprinting"). Most recommend colonoscopy with biopsies, but this is contraindicated in the presence of severe symptoms or inflammation. Sometimes, an abbreviated sigmoidoscopy for examination and biopsy is clinically indicated. In the acutely ill child with colitis, perform a flexible sigmoidoscopy rather than a barium enema. The advantage of the sigmoidoscopy is that it allows for mucosal biopsies that are diagnostic.

Treatment of UC

Lifelong Treatment

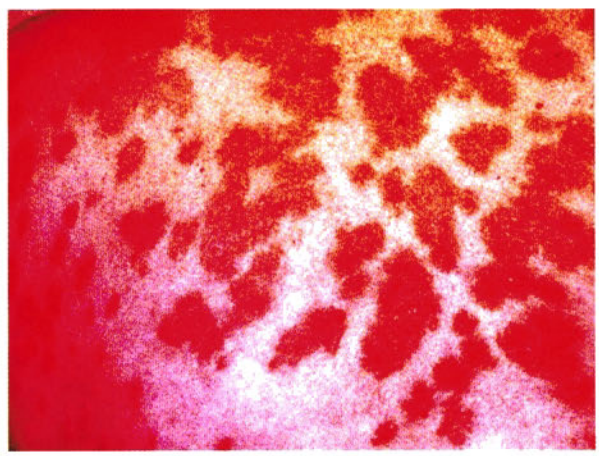
Treatment is lifelong and includes a variety of agents.

5-aminosalicylates

Sulfasalazine was one of the first 5-aminosalicylates used and is composed of 5-aminosalicyclic acid linked by an azo bond to sulfapyridine. It is the 5-aminosalicyclic acid that is the active antiinflammatory agent. Nausea and headache are common side effects and are related to the sulfapyridine. Newer agents (mesalamine, olsalazine, etc.) without the sulfa component are available but are more expensive. Removing the sulfa component has reduced the side-effect profile for these agents. Most patients with mild-to-moderate UC respond very well to sulfasalazine. After remission has been attained, many can be maintained on mesalamine. Suppository and enema forms are also available and work well for those children with distal disease.

Corticosteroids

Corticosteroids are very effective in relieving symptoms and treating moderate-to-severe UC. Corticosteroids are indicated only for short-term induction and treatment of disease "flares." Long-term use is associated with significant side effects, including hyperglycemia, osteoporosis, osteonecrosis, myopathy, susceptibility to infection, cataracts, growth retardation, behavioral



Courtesy of CDC Lucille K. Georg, MD

Image 14-12: Erythema Nodosum

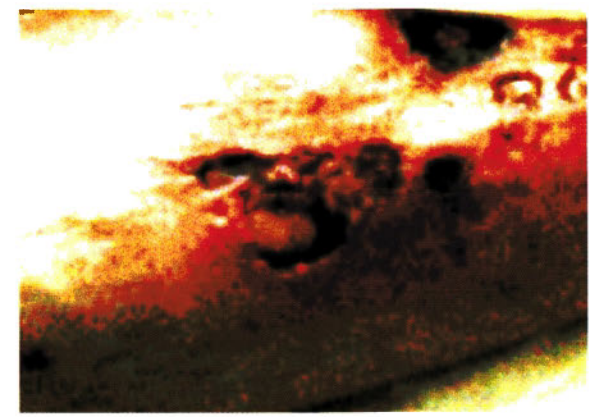


Image 14-13: Pyoderma Gangrenosum

Quick Quiz

- What methods and drugs are used to treat UC?
- In what part of the GI tract does Crohn disease occur?

problems, acne, striae, and cushingoid appearance. You also can use topical hydrocortisone enemas and foam for distal colon disease, but these can cause adrenal suppression with prolonged use. Newer topical agents, such as budesonide and fluticasone, have much less adrenal-suppressive effects.

Purine Analogs

6-mercaptopurine (6-MP) and azathioprine are very effective in maintaining remission for severe UC and Crohn disease. They have a very slow onset of action (3–6 months) and thus are not appropriate as first-line drugs for a severe acute flare. Both drugs are purine analogs and have cytotoxic and immunosuppressive properties. They inhibit the proliferation and function of leukocytes. Severe complications are rare, but elevated liver enzymes and/or leukopenia occur in about 15% of patients and resolve with lowering the dose of the drug. Metabolite testing is now available for these agents and can be used to ensure levels are not in a range associated with these complications. Discontinue use if hypersensitivity reactions occur, which present as skin rashes, recurrent fevers, or pancreatitis.

Cyclosporine A

Cyclosporine A inhibits the production of proinflammatory cytokines by T-helper cells. Most use it with patients who have severe UC that is refractory to standard therapy. Relapse rates, however, are very common in the first year, and serious side effects (liver toxicity, neurotoxicity, hypomagnesemia, hypertension, renal toxicity, gingival hyperplasia, and hirsutism) are a concern.

Methotrexate

Methotrexate inhibits hydrofolate reductase, which impairs DNA synthesis. It also inhibits cytokine production and causes T-cell apoptosis. It works well initially but does a poor job of maintaining remission. Methotrexate is reserved for those who are not surgical candidates for cure and who cannot tolerate or have difficulties with azathioprine or 6-MP.

Biologic Agents

Infliximab is a chimeric IgG1 monoclonal antibody that is directed against tumor necrosis factor (anti-TNF-α). This is now widely used in children that do not respond to the immunomodulator agents. It is given by intravenous infusion typically at 8-week intervals. Because it is a chimeric protein, the primary side effect is an allergic reaction to the protein. This can be immediate or a delayed serum sickness. The effect of the agent also appears to fade with time in some patients. Other "mabs" are available as well, but generally, if the patient reaches this point, they will be managed by a specialist.

Other Agents

Antibiotics have no beneficial effect in UC unless a specific indication, such as sepsis or abscess, is noted. With the initial presentation or flare of the disease, look for *C. difficile* and treat it if found.

Antidiarrheal agents should not be routinely used in pediatric UC.

Bowel rest is not generally indicated. Use of fish oils containing ω (omega)-3 fatty acids has lessened disease activity in some preliminary reports.

Surgical Therapy

Emergent surgery may be needed as a life-saving procedure. Emergently the patient may require an ostomy. Long-term, most now eventually progress to an ileo-anal pull-through operation, with creation of a surgical "pouch," which preserves continence. Indications for urgent surgery include uncontrollable massive bleeding, perforation, and toxic megacolon. Most often, though, surgery is done because of failure of standard medical therapy. Consider elective surgery in those with steroid dependence; intolerance of, or complications from, immunosuppressive therapy; long-standing disease; or evidence of colonic dysplasia or cancer.

After pull-through surgery, "pouchitis" may occur, which consists of increased stool frequency, lower abdominal pain, tenesmus, and hematochezia. Most believe this is caused by colonization of the ileal mucosa-lined pouch with colonic flora. Metronidazole appears to manage pouchitis well.

Ulcerative Colitis and Colon Cancer

UC predisposes to colon cancer at an increasing rate that is correlated with the duration of active disease. After 10 years of active disease, the yearly risk of colon cancer is about 1%. Children and adolescents with UC should undergo colonoscopy with biopsy biannually after having the disease for 7 years. If dysplasia is found, colectomy is indicated.

CROHN DISEASE

Overview

Crohn disease is an inflammatory process that is transmural, involving the GI tract anywhere from mouth to anus. Bowel segments can be inflamed with intervening normal mucosal involvement, referred to as "skip lesions." The most common site for Crohn disease is the terminal ileum, with nearly 70% of pediatric patients

also having some colon involvement (usually the cecum and/or ascending colon). Aphthous ulcers are suggestive of Crohn disease. Extraintestinal manifestations are common and may precede the GI symptoms for years. Crohn disease is seen mainly in adolescent children. It has a higher prevalence in Ashkenazi Jews.

Genetics is a major risk factor. If both parents are affected, the risk of having an affected child is about 1/3. Monozygotic twin studies show a very strong concordance for Crohn disease—far greater than for UC.

Recent studies have found increased antibodies to *Saccharomyces cerevisiae* in about 60% of patients with Crohn disease. Etiology, however, is still unknown (for this and UC). However, the *NOD2* gene, which regulates monocyte response to antigens, has been found to be associated with Crohn disease.

Weight loss and growth failure are much more common with Crohn disease than with UC. Anal fistulae and abscesses are commonly seen in Crohn patients.

Crohn disease is transmural and results in fistulous tracts as well as strictures. On microscopic examination, you will see a chronic granulomatous inflammation involving all layers of the intestinal wall. Noncaseating granulomas that contain multinucleated giant cells and epithelioid cells are pathognomonic for Crohn disease although only seen 40% of the time.

If the small intestine and the colon are both involved, Crohn disease is the diagnosis. What is difficult is when Crohn disease involves only the colon. Colonoscopy with biopsy is the best means for diagnosis. Infectious etiologies (tuberculosis, histoplasmosis, etc.), lymphomas, and sarcoidosis are in the differentials.

Treatment

Basis for Therapy

Managing Crohn disease is more difficult than managing UC, and, unlike UC, surgical therapy is not definitive. Therapy is based on clinical symptoms and does not necessarily correlate with endoscopic or histologic findings.

5-aminosalicylates

Sulfasalazine or a mesalamine product appear to be most useful for those with ileocolonic or colonic Crohn disease but do not work well for those with isolated small intestinal disease. The 5-aminosalicylate products work for inducing remission in those with mild-to-moderate Crohn disease.

Corticosteroids

Corticosteroid therapy provides marked improvement in patients with active Crohn disease. Most usually give prednisone for 3–4 weeks until remission is achieved; then attempt a gradual weaning, along with therapy of mesalamine and/or 6-MP. Steroids for maintenance therapy are not supported by data, and long-term side effects are significant.

Purine Analogs

Use of 6-MP or azathioprine will usually result in remission and allow you to avoid long-term corticosteroids. It can take 3–6 months before they become effective, due to their slow onset of action. Many children with Crohn disease are maintained on these agents until early adulthood. Therapeutic metabolite levels can be monitored to avoid complications.

Methotrexate

Reserve methotrexate for those children who fail to respond to, or have significant complications with, 6-MP or azathioprine. Crohn disease can respond very well to methotrexate if other agents present problems.

Antibiotics

Antibiotics are more commonly used with Crohn disease than with UC. Many use metronidazole for the fistulae and perianal abscesses that occur. Side effects include nausea, appetite loss, and complaints of a metallic taste. Prolonged use can result in paresthesias, which can persist for years after stopping therapy.

Ciprofloxacin has recently shown benefit comparable to metronidazole. Combination therapy of ciprofloxacin and metronidazole is very effective in treating fistulae and perianal disease.

The therapeutic effect of antibiotics tends to fade with time, therefore; antibiotic therapy is reserved for short-term use in the conditions indicated.

Infliximab

Infliximab is a chimeric IgG1 monoclonal antibody that is directed against tumor necrosis factor (anti-TNF-α). It is the first biological agent approved by the FDA for clinical use in patients with steroid-refractory intestinal or perianal Crohn disease. It is widely used in those patients refractory to standard therapy. There are several studies using other biologic agents in Crohn disease, but these are not standard practice at this time. However, they may be utilized when the response to infliximab fades. These patients will generally be managed by a specialist and is outside the scope of what you'll be tested on a general pediatrics exam.

Nutritional Concerns

Unlike UC, Crohn disease responds to bowel rest. Recommend an elemental diet for 1 month, excluding other food. Early relapse occurs if the diet is ended.

Quick Quiz

- Which is more likely to cause weight loss and growth problems, Crohn's or UC?
- Which is transmural—Crohn's or UC?
- Is surgical therapy curative for Crohn disease?
- What is the most common surgical emergency in children?
- If the pain of appendicitis suddenly resolves, what has likely happened?

Once remission has occurred, recommend a cycle of elemental diet 1 out of every 4 months. This option requires a highly motivated patient who wishes to avoid alternative therapies.

Supplement nocturnal nasogastric feedings with elemental or other formulas to reverse growth failure. Osteoporosis is also of significant concern in children with Crohn disease and supplementation with calcium and vitamin D is recommended.

Surgical Therapy

Surgical therapy is not curative for Crohn disease, and it will eventually recur in the residual bowel. Before more conservative surgical approaches became the norm, Crohn disease was a leading diagnosis resulting in short bowel syndrome. Surgery is mainly reserved for complications, such as massive hemorrhage, perforation, and fulminant colitis, which fail to respond to medical management. Fistulae may require surgery. Some resect severely affected areas of the bowel, particularly the terminal ileum, to reduce symptoms. Rectal involvement may require a fecal diversion, such as an ileostomy or colostomy.

Crohn Disease and Colon Cancer

Crohn disease is much less likely than UC to induce colon cancer, but the rate of colon cancer is still 20x higher in patients with Crohn disease compared to the normal population. Those patients with > 10-year history of Crohn disease should undergo yearly colonoscopy.

APPENDICITIS

Overview

Appendicitis is the most common surgical emergency in children. The peak age of onset is 12 years of age; it is unusual before 2 years. In about 1/3 of cases, the appendix will rupture before surgery; this occurs much more rapidly in children.

In children, fatigue and anorexia are frequently the common symptoms at initial presentation. This may accompany indigestion, which is followed by periumbilical discomfort. Soon after, fever between 100° and 102° F, with nausea and vomiting, occurs. Over several hours, the inflammation involves the parietal peritoneum and localizes to the right lower quadrant of the abdomen. Depending on the location of the appendix, the pain can be in different locations: pelvic appendix—hypogastric pain; retrocecal appendix—psoas and obturator muscle pain; retrocolic appendix—right flank pain.

Pain that suddenly resolves usually indicates rupture, which has relieved the appendix's pressure. Soon, however, high fever, persistent vomiting, thirst, and signs of peritonitis develop. Signs of systemic infection may occur; or the infection may be "walled off," and a local abscess may form.

Early on, the patient may not have a lot of pain and can be in minimal distress. However, consistent, localized, right lower quadrant tenderness and guarding eventually become prominent. You must perform a rectal examination to search for pelvic appendicitis. You would see psoas irritation with extension of the thigh, and obturator irritation with passive internal rotation of the thigh. Rovsing sign occurs when abdominal palpation remote to McBurney's point results in right lower quadrant pain.

Most inflamed appendices will perforate within 24–48 hours after onset. CBC is not specifically helpful, but microscopic pyuria and hematuria may be associated with appendicitis. Always perform a pregnancy test in any adolescent who has the potential to ovulate. Abdominal x-ray is rarely helpful, unless it shows a fecalith.

Treatment of Appendicitis

Admit for observation if the diagnosis is unclear, and preferably have the same physician conduct serial examinations. Ultrasound can sometimes be helpful. Otherwise, consider a barium enema. If the appendix fills normally and empties completely, you can rule out appendicitis. Alternatively, some suggest a CT to investigate the appendix since it is more sensitive than the barium enema, although it has a significant radiation exposure.

Treatment is geared to early diagnosis and early appendectomy. If the appendix is not ruptured, simply remove it and patients generally can go home in 12–24 hours. If rupture has occurred, conduct intraoperative anaerobic and aerobic cultures, irrigate the peritoneal cavity, and place drains if abscesses are present. Give broad-spectrum IV antibiotics until the patient is afebrile and clinically improved.

In some patients, perforation occurs days prior to presentation, and you will notice a palpable mass in the right lower quadrant. If the child is well without evidence of peritonitis, manage conservatively with

antibiotic therapy and observation. Appendectomy can be done 4–6 weeks later, or sooner, if there is no response to the antibiotics.

Complications are rare today but can include wound infection and intraabdominal abscess.

Chronic Appendiceal Pain

The following 3 conditions are hypothesized to cause chronic appendiceal pain:

1) Chronic appendicitis—a rare cause of inflamed appendices; refers to a chronically inflamed appendix filled with mononuclear cells.
2) Recurrent appendicitis—refers to a once-inflamed appendix that has slowly resolved spontaneously but with focal appendiceal fibrosis.
3) Appendical colic (controversial because some pediatric surgeons question whether this condition even exists)—results from appendiceal cramping against an intraluminal obstruction (fecaloma, adhesion, foreign body, parasite, carcinoid or lymphoid hyperplasia). Pain occurs in the early morning on arising and after eating or drinking. Appendectomy will alleviate the pain and symptoms, but pain recurs in about 50%.

TYPHLITIS

Typhlitis, also known as inflammation of the cecum, is mainly seen in patients who are treated for leukemia during periods of neutropenia. It can occur in other immunodeficiencies and after organ transplant. It is dangerous in that the inflammation can progress rapidly to gangrene or perforation. Fever and right lower quadrant pain usually suggest acute appendicitis. Abdominal x-ray may show bowel wall thickening or pneumatosis intestinalis. Most use CT to investigate. Treat with bowel rest, IV fluids, and antibiotic therapy. Some recommend WBC transfusions. Almost all resolve without surgical intervention, unless perforation occurs. Once typhlitis occurs, it has a high risk for recurrence with subsequent episodes of neutropenia.

JUVENILE POLYPS AND JUVENILE POLYPOSIS

Juvenile polyps occur in about 1% of preschool children and account for the majority of all polyps in children. Just what the heck are juvenile polyps? They are inflammatory polyps, usually pedunculated hamartomas that look like a raspberry on a stalk. The classic presentation will be a 4–6-year-old child who presents with intermittent, painless rectal bleeding with bowel movements. There is no history of a familial polyp syndrome, and there will typically be fewer than 5 polyps. Solitary juvenile polyps of this type are not cancer-prone.

On the other hand, juvenile polyposis occurs when there are more than 6 juvenile polyps, and these have a high, long-term risk of malignancy. Juvenile polyposis coli (involving only the colon) refers to polyps that are distributed throughout the colon. If a family member has already been diagnosed with juvenile polyposis, any other member who has even a single juvenile polyp is considered to also have juvenile polyposis.

Generalized juvenile polyposis, which involves having polyps throughout the GI tract, is very rare and presents in infancy or very early childhood. It can present as rectal bleeding, diarrhea, anemia, rectal prolapse, and intussusception. With this disorder, there are hundreds of polyps in the stomach, small bowel, and large bowel. Risk of eventual malignancy is extremely high.

Most use colonoscopy in all children with rectal bleeding. It allows you to assess for the presence of polyps, as well as the number and distribution, and to get histological data. Unless a large number of polyps are found, remove all polyps for histology. If you find a single rectosigmoid polyp with typical histology, no further evaluation is necessary. If 5 or more juvenile polyps are found, or if a juvenile polyp with adenomatous changes is found, perform colonoscopy every 6–12 months until no polyps are found; check every 2 years thereafter if no further polyps develop. Monitor children with 2–4 polyps with a repeat colonoscopy. For any child with polyps that show adenomatous changes, you must conduct further investigations.

PEUTZ-JEGHERS SYNDROME

Peutz-Jeghers syndrome is an autosomal dominant disease (mutation of the *STK11* gene on chromosome 19p) with variable penetrance. It presents with GI hamartomatous polyps and mucocutaneous hyperpigmentation. The lesions are brown-black macules, 1–5 mm in diameter, and look like freckles. They are nearly universally on the lips and buccal mucosa and are less commonly found on the nose, hands, and feet (Image 14-14). The lesions occur during infancy and childhood and fade during adolescence. Patients have multiple polyps throughout their GI tract. Most commonly affected is the small bowel, followed by the colon and the stomach. Rarely, polyps may be found in the bronchi and GU tract. Histologically, they are distinguished from juvenile polyps by the presence of smooth muscle bands within the polyp.

About 1/3 of patients are diagnosed during childhood, but the mean age of onset of symptoms is around

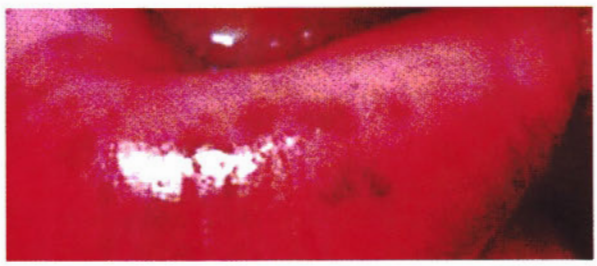


Image 14-14: Peutz-Jeghers Syndrome

QuickQuiz

- What is typhlitis?
- How does Peutz-Jeghers syndrome present?

22 years of age. The most common presentation is intermittent, colicky, abdominal pain, with intestinal obstruction from intussusception, GI bleeding, and anemia. Nearly 1/2 of patients develop cancers outside of the colon during their lifetime, with the most common involving breast, cervix, ovary, testicle, and pancreas. 2–13% develop colon cancer. Adenomatous changes are found in about 5% of Peutz-Jeghers polyps.

Diagnosis depends on finding the hamartomatous polyps, recognizing the skin lesions, and discerning a family history. Remove all large polyps, and perform surveillance endoscopy to remove future polyps. Also survey for other tumors beginning in patients at age 10, or sooner if symptoms have already developed. Screen all 1st degree relatives regularly after 10 years of age.

SYNDROMES LINKED TO *PTEN* GENE MUTATIONS

What Are *PTEN* and MATCHS?

These are recently described rare syndromes now known by the term PTEN-MATCHS syndrome. *PTEN* refers to the protein tyrosine phosphatase gene and MATCHS refers to Macrocephaly, Autosomal dominant, Thyroid disease, Cancer, Hamartoma, and Skin abnormalities.

Ruvalcaba-Myhre-Smith Syndrome

Ruvalcaba-Myhre-Smith syndrome is characterized by macrocephaly, pigmented penile lesions, and hamartomatous intestinal polyps. The polyps present with rectal bleeding and abdominal pain. Additional findings include café-au-lait spots, lipomas, retardation, and a lipid-storage abnormality.

Cowden Syndrome, Bannayan-Zonana Syndrome, and Bannayan-Riley-Ruvalcaba Syndrome

These 3 syndromes are all very rare and are characterized by having multiple hamartomas of the skin, mucous membranes, breast, and thyroid. Hyperkeratotic papillomas of the lips and tongue are characteristic. They are caused by a mutation on the *PTEN* tumor suppressor gene on chromosome 10g22-23.

Proteus Syndrome

Proteus syndrome is a rare disorder with hamartomatous polyps and hemihypertrophy, gigantism of the extremities, angiomas, pigmented nevi, and multiple lipomas or hamartomas. Recognize this one on the Board exam if they describe a patient with hemihypertrophy and hamartomas.

FAMILIAL ADENOMATOUS POLYPOSIS SYNDROMES

Incidence

Familial adenomatous polyposis syndromes are due to mutations on chromosome 5q21-22 and occur in about 1/10,000 births. Most are autosomal dominant with variable penetrance and present with hundreds of GI adenomatous polyps. About 1/3 will present as a new mutation without a family history. Gardner (see next) is the most commonly described (and is often tested on the Boards).

Gardner Syndrome

Gardner syndrome is characterized by having extraintestinal tumors. The term "polyposis coli" used to be considered a separate disease entity, but now it appears that polyposis coli has the same gene mutation as Gardner syndrome, and almost all of those with polyposis coli have extraintestinal manifestations as well. The occurring soft tissue tumors include desmoid tumors, sebaceous and epidermoid cysts, lipomas, and subcutaneous fibromas. Osteomas of the skull, maxilla, and mandible are common as well. Other associations include supernumerary teeth and congenital hypertrophy of the retinal pigment epithelium.

Diagnosis is confirmed by finding the hundreds of adenomatous polyps or by genetic testing.

Management is controversial, but most recommend yearly screening with colonoscopy, beginning between 10 and 12 years of age. Treatment with cyclooxygenase inhibitors has been shown to suppress polyp expression and patients are now maintained on sulindac. Periodic evaluation of the upper GI tract, as well as the thyroid gland, is also recommended because of the increased risk of cancers in these areas.

OTHER TUMORS

Neurofibromas

Neurofibromas are commonly associated with café-au-lait spots and skin tumors, but up to 25% of patients with von Recklinghausen disease also have GI tumors. Most commonly, they are in the small intestine. They can cause abdominal pain, bleeding, and anemia.

Adenocarcinoma

Adenocarcinoma is rare in childhood. It usually has histologic features of mucin-producing or signet-ring varieties. CEA is not a reliable marker in children.

Children usually have a concomitant risk factor, such as a familial polyposis syndrome, inflammatory bowel disease, or ureterosigmoidostomy (performed due to exstrophy of the bladder). The latter develop cancer at a rate of 5%, so perform surveillance endoscopy with biopsy every 2–3 years in these patients.

Lymphoma

In children, lymphoma is the most common malignant tumor of the small intestine. These occur in the 2nd decade and are almost always Burkitt lymphoma (non-Hodgkin's). The terminal ileum and cecum are the most common sites. *Helicobacter pylori* is a known risk factor for gastric lymphoma. Celiac disease also predisposes to small intestinal lymphomas. Post-transplant lymphoproliferative disease is associated with EBV infection.

Carcinoid

Carcinoid is very rare in children. Benign carcinoid tumors of the appendix are more commonly seen than malignant tumors, which predominate in the ileum and have liver metastases. The tumors are made up of neuroendocrine cells that release catecholamines, bradykinins, and serotonin—substances that can result in flushing and diarrhea. The benign appendiceal form can be cured with appendectomy. The malignant form does not respond well to therapy. You can control some symptoms with octreotide, which is a long-acting analog of somatostatin.

ABDOMINAL WALL DEFECTS

OCCURRENCE

Abdominal wall defects are varied in appearance and location. They are fairly rare, occurring in only about 1/5,000 live births.

OMPHALOCELE

Omphalocele is a defect in the abdominal wall at the umbilicus and can contain both hollow and solid visceral organs. Omphaloceles are larger than 4 cm and are covered by peritoneal membrane internally and amniotic membrane externally. In contrast, umbilical hernias are smaller than 4 cm and contain only intestine.

About 50–75% of neonates with an omphalocele have an associated congenital anomaly, including the thoracoabdominal syndrome (known as the pentalogy of Cantrell), lower midline syndrome, and Beckwith-Wiedemann syndrome. About 25% have major chromosomal abnormalities, including the trisomies.

Omphalocele presents as a central defect of the umbilical ring and has the abdominal contents inside a sac. The umbilical cord inserts into the sac. In about 1/2, the sac contains the stomach, loops of small/large intestines, and liver. "Giant" omphaloceles present with large/small intestines, liver, spleen, gonadal tissue, and bladder in the sac. About 10–20% of omphaloceles will rupture *in utero* and may present more like gastroschisis (see below) with thickened bowel covered in exudate. Midgut volvulus is common in omphalocele.

Manage by keeping the infant warm and hydrated. Cover exposed omphalocele with plastic wrap and warm, saline-soaked gauze. The bowel should be fixed so that circulation is well maintained. Immediately begin IV antibiotics. Nonoperative management is acceptable if the infant is too ill for surgery. Apply antiseptic agents, such as silver nitrate or povidone-iodine, to the omphalocele. These will eventually become an eschar and epithelize, thus protecting the exposed organs. Once this has become granulated, you can place a skin graft, resulting in a ventral hernia, which can be repaired in the future. If primary surgical repair cannot be done, you can attempt a staged repair. Survival of infants with omphalocele is 75–95%. Survival is usually affected by the associated congenital anomalies.

GASTROSCHISIS

Gastroschisis presents as a 2–5 cm abdominal wall defect to the right of the umbilicus, with exposed loops of small and large intestines that are short and thick due to an inflammatory reaction of the serosa. The solid visceral organs usually are contained in the abdominal cavity, and the umbilical cord is normal. Gastroschisis is more common than omphalocele and is commonly associated with midgut volvulus.

Initial management of gastroschisis is similar to that of omphalocele, with resuscitation, hydration, and temperature control. Perform a similar plastic bag/gauze procedure. For gastroschisis, surgery is mandatory and cannot be delayed. Primary surgical closure is frequently successful in gastroschisis. Early postoperative complications include necrotizing enterocolitis and intestinal obstruction. The survival rate for gastroschisis is 95%.

ANORECTAL DISORDERS

OCCURRENCE

Anorectal disorders occur in about 1/4,000 births and can be minor to severe. It is probably easiest to think of these separated out by sex, since the defining characteristics of each disorder depend upon the sex of the patient. Generally, those disorders that cause severe deformity or absence of the sacrum will result in serious abnormalities and lack of sphincter tone. Also, absence of 2 or more vertebrae is associated with severe continence problems.

Congenital anorectal disorders are often part of other disorders, including VATER (Vertebrae, Anus, Trachea

QuickQuiz

- In children, what is the most common malignant tumor of the small intestine?
- What is an omphalocele?
- If an omphalocele is present, should you suspect another congenital anomaly or is it likely an isolated event?
- What is a gastroschisis?

and Esophagus, Radius and Renal anomalies) and VACTERL (Vertebrae, Anal atresia, Cardiac abnormalities, TracheoEsophageal fistula, Renal anomalies, and Limb anomalies).

MALE ANORECTAL DISORDERS

Perineal Fistula

A perineal fistula presents with a small orifice on the perineum located just anterior to the center of the external orifice. Usually, it is close to the scrotum. Boys will have a "bucket handle" malformation or "black ribbon" structure in their perineum that is a subepithelial fistula filled with meconium. Anal dimples are prominent. Less than 10% of those affected will have other organ abnormalities. The defect can be repaired without a colostomy.

Rectourethral Fistula

A rectourethral fistula is the most common anorectal defect in males. A rectourethral fistula occurs when the rectum communicates with the lower (bulbar) or upper (prostatic) part of the urethra. Most patients have a well-defined midline perineal groove and an anal dimple. A protective colostomy is required during the newborn period with complete surgical repair later in life.

Rectovesical Fistula

A rectovesical fistula occurs when the rectum communicates with the bladder neck. The sacrum is frequently absent. Bowel function is poor, and a colostomy is required during the newborn period, followed by corrective surgery later in life.

FEMALE ANORECTAL DISORDERS

Perineal Fistula

As in boys, a perineal fistula is also the simplest defect in girls. It is very similar in girls, except that the small orifice is located close to the vulva in the female. It does not require colostomy, unlike the other anorectal disorders that affect females.

Vestibular Fistula

Vestibular fistula is the most common defect in girls. In this instance, the rectum opens in the vestibule of the female genitalia immediately outside the hymenal orifice. The sacrum and sphincter tone are normal, and an anal dimple is present. You must perform a protective colostomy in the newborn period before definitive surgery can be done.

Persistent Cloaca

Persistent cloaca means that the vagina, rectum, and urinary tract meet and fuse as a common channel. There is a single orifice just behind the clitoris. The length can vary from 1 to 10 cm. Those with short channels (< 3 cm) have a well-developed sacrum and good sphincter tone. Those with longer channels (> 3 cm) have a more complex defect and usually have a poorly defined sacrum and sphincter tone. Most girls with a cloaca have an abnormally large vagina filled with mucus (hydrocolpos).

You must perform a colostomy in the newborn period; 90% also have urologic abnormalities requiring emergent attention.

ANORECTAL DISORDERS PRESENTING SIMILARLY IN BOTH SEXES

Imperforate Anus without Fistula

An imperforate anus occurs when the rectum is completely closed off and does not communicate with the anus or skin. On average, the rectum is found about 2 cm above the perineal skin. The sacrum is well developed, and the sphincteric mechanism is intact. Eventual prognosis is good with an initial colostomy in the newborn period and eventual reparative surgery later. Children with Down syndrome have a much higher incidence of imperforate anus than other children. Some children have much higher defects anatomically, which result in more difficulty with long-term dysfunction.

Rectal Atresia

Rectal atresia is one of the rarest anorectal abnormalities. These patients have a normal anal canal and a normal anus. You will frequently find the defect when you attempt to use a rectal thermometer. Obstruction is present about 2 cm above the skin level. A protective colostomy is necessary in the newborn period, followed by reparative surgery at a later date.

Rectal Prolapse

Rectal prolapse occurs when one or all layers of the rectum protrude through the anus. Usually, it is just mucosa that prolapses, and it presents as a red-purple, circular protrusion from the anus. It is

common for a small amount of rectal mucosa to prolapse after normal defecation. If all layers prolapse, this is known as procidentia. Luckily, it is rare. It presents as a protrusion with circumferential folds due to the contractions of the circular musculature of the prolapsed rectum.

Mucosal prolapse is most common in those under 2 years of age because of the flat sacrum and weak pelvic floor muscles. (There have been reports of massive intestinal prolapse in children sitting on unprotected swimming pool drains—not a likely Boards topic but interesting for cocktail conversation among medicos.) Cystic fibrosis is always key to remember with rectal prolapse, but remember: CF is not the most common cause; it actually comes in 3rd overall. Constipation is #1, followed by diarrhea at #2. Other etiologies include various neuromotor disorders, and nearly 20% have no identifiable cause. Most mucosal prolapses reduce spontaneously, but the anus can gap open for up to an hour after reduction. Some will require surgical intervention, but these are exceedingly rare. In children with a history of recurrent rectal prolapse, the anus and anorectal manometry appear normal. Treat any underlying condition (for example, constipation or diarrhea—or prevent the kid from sitting on that swimming pool drain!). Again, surgery is rarely needed.

Anal Fissures

Anal fissures are the most common cause of rectal bleeding in infants. They are slit-like tears of the anal canal, usually located on the posterior or anterior anal verge. Frequently, they are due to the passage of large stools in a constipated infant. After the fissure heals, a small anal tag may remain. In the older child, when the anal fissure does not heal with stool softeners, warm sitz baths, and generous lubrication to the anal skin, suspect Crohn disease. If there are multiple anal fissures or signs of genital trauma, suspect sexual abuse.

Perianal Itching (Pruritus Ani)

Perianal itching, also known as pruritus ani, is very common and frequently due to perianal dermatitis or infection. *Candida* overgrowth commonly occurs after a course of antibiotics for otitis media, etc. Other etiologies include atopic dermatitis, contact dermatitis, perianal streptococcal infection, and anal fissures. Pinworms and tapeworms may present with perianal itching. Some foods—including tea, coffee, chocolate, soft drinks, citrus, tomatoes, and chili—contain chemicals that irritate the skin or have histamine releasers. Urinary tract infection may present in the younger child as itching.

Perianal streptococcal infection presents as an "angry," bright red, confluent rash around the anal orifice and can spread throughout the entire perineal area. Impetigo-like lesions present as classic honey-colored crusts. Rectal bleeding occurs, and you may discover that a recent streptococcal disease occurred in the household. Occasionally, the affected child will have a concomitant streptococcal pharyngitis. Use oral penicillin for cure. Topicals are ineffective.

HIRSCHSPRUNG DISEASE

OCCURRENCE

Hirschsprung disease (congenital aganglionic megacolon) will be given special attention here, because it so often appears on the Board exam. One reason is that Hirschsprung disease is the most common cause of lower intestinal obstruction in neonates! It occurs in 1/5,000 births and is due to the absence of enteric ganglionic neurons (aganglionosis) that begins at the anus and then extends proximally for a varying distance. In 75% of those affected, aganglionosis is limited to the rectum and sigmoid. But about 8% will have total colon involvement, and an even smaller number will have the rarest form of aganglionosis, that which is present throughout the whole small intestine. There are also concerns in constipated adolescents and adults for the possibility of "short-segment" Hirschsprung's.

The rectosigmoid form of the disease has a male predominance of 4:1. This form has a multifactorial or a recessive pattern of inheritance. The risk of an affected sibling having the disease is about 7%. Racial differences are not noted. As the affected intestinal segment length increases (for example, involving the total colon or intestine), the sex differences decrease, and the sibling risk increases to nearly 20%. There is an increased association with Down syndrome, Laurence-Moon-Bardet-Biedl syndrome, Smith-Lemli-Opitz syndrome, and Waardenburg syndrome.

PATHOGENESIS

Hirschsprung disease occurs when the craniocaudal migration of neural crest cells fails to happen. Various factors affect the migration of the neural crest cells, and it is felt that expression of these molecules is controlled by the Hox and Sox homeobox genes. (Sounds like a Dr. Seuss book!) In particular, 2 signaling systems have been noted: ret/glial-derived neurotrophic factor and endothelin receptor B/endothelin 3. Many families with Hirschsprung disease have abnormalities in the genes that encode these signals. Additionally, other factors, as yet unknown, also mediate the failure of the neural crest cells to develop and/or migrate properly.

Because of the loss of normal innervation of the rectum, there is an "overexpression" of extrinsic parasympathetic and sympathic nerves in the lamina propria and muscularis mucosae. Histologically, this appears as an absence of Meissner and Auerbach plexus and hypertrophied nerve bundles, with high concentrations of acetylcholinesterase between the muscular layers and

Quick Quiz

- What are the 3 most common causes of rectal prolapse?
- What is the etiology of Hirschsprung disease?
- A biopsy will show histologic absence of what structures in a patient with Hirschsprung's?
- A term infant is 48 hours old and has not passed a meconium stool; is it necessary at this point to evaluate for Hirschsprung's?
- How does enterocolitis present in infants with Hirschsprung's?
- What is the most accurate procedure with which to diagnose Hirschsprung's?

in the submucosa. This causes the aganglionic segment, internal sphincter, and anal canal to remain constantly contracted, resulting in obstructive symptoms. The area proximal to the aganglionic segment is dilated and hypertrophied.

CLINICAL PRESENTATION

The diagnosis of Hirschsprung disease is usually made during the neonatal period, but some are not diagnosed until 3 years of age or later, with reports of patients well into adulthood. Three presentations are noted:

1) Delayed passage of meconium
2) Intestinal obstruction
3) Enterocolitis

90% of normal, full-term infants will pass meconium within 24 hours, and 99% within 48 hours. In children with Hirschsprung disease, 94% fail to pass meconium within the first 24 hours. Therefore, evaluate for Hirschsprung disease any term infant that does not pass meconium within 48 hours of birth.

Complete intestinal obstruction can occur in the newborn—or may occur later in the older infant who has a history of only constipation. Intestinal obstruction is accompanied by bilious vomiting, obstipation, and massive abdominal distention.

Enterocolitis usually occurs during the 2nd to 4th weeks and is characterized by fever with explosive, foul-smelling stools. Bloody diarrhea is common, as is abdominal distension. The prognosis for enterocolitis is poor, and the mortality rate can be as high as 33%. The pathogenesis of enterocolitis is unknown. Delayed diagnosis is the contributing factor for many cases of enterocolitis.

DIAGNOSIS

Once you suspect Hirschsprung's, proceed quickly with diagnostic evaluation. The longer it takes for a diagnosis to be made, the more likely enterocolitis may occur. The most accurate tool today is the suction rectal biopsy. Perform the biopsy no closer than 2 cm to the dentate line to avoid the normal area of hypoganglionosis at the anal verge. Acetylcholinesterase staining will show hypertrophied nerve trunks in the mucosal and myenteric plexuses and their presence in the muscularis mucosa. However, in total colonic aganglionosis, the acetylcholinesterase activity is not uniformly increased, and you may not observe the thickened nerve trunks; therefore, their absence does not rule out disease. Biopsy in this case must contain adequate submucosa to reliably diagnose the absence of enteric neurons.

The diagnosis is based on the absence of any ganglion cells detected in a biopsy containing adequate submucosa. If the diagnosis is still questionable, do a full-thickness rectal biopsy to look for aganglionosis in the mesenteric and submucosal plexuses. Barium enema was used in the past and is now viewed as unreliable for accurate diagnosis, but it is still useful for showing areas of transition and extent of disease (Image 14-15).

Additionally, anorectal manometry is extremely accurate in the hands of those experienced with it. Failure of the internal anal sphincter to relax in response to distension of the rectum (rectosphincteric reflex) is diagnostic of Hirschsprung disease.

Other syndromes on the differential include meconium plug syndrome, other nerve and muscle disorders of the lower colon, hypoganglionosis, and hollow visceral myopathy.

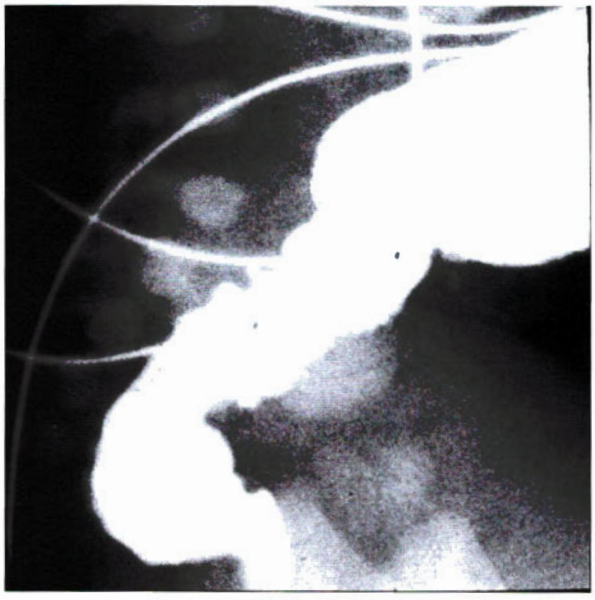


Image 14-15: Hirschsprung Disease

TREATMENT

If the infant presents with an obstruction, create a stoma proximal to the aganglionic segment. You must treat enterocolitis with fluid management, broad-spectrum antibiotics, nasogastric decompression, and warm saline rectal washouts to help with colonic decompression. Once the patient is stable, perform a proximal colostomy.

Surgical management of Hirschsprung's usually involves 1 of 3 surgical techniques:

1) Swenson
2) Duhamel
3) Soave procedures

Each involves resection of the aganglionic bowel, then a reanastomosis of the proximal normal bowel to the normal anal canal. The differences depend on how the bowel is reconstructed. Most recommend early repair and reconstitution of the bowel, though some recommend waiting until 6–12 months of age.

Complications after surgery include stricture or leakage at the anastomotic site, as well as pelvic abscesses.

PSEUDO-HIRSCHSPRUNG DISEASE

Pseudo-Hirschsprung disease refers to various disorders that may affect the submucosa and myenteric plexuses—and can affect limited or widespread areas of the GI tract. The diseases can be due to defects of the smooth muscle coats or of the GI nerves themselves.

Hypoganglionosis

Hypoganglionosis can be congenital or acquired and occurs when the number of myenteric neurons is decreased. The congenital form likely is due to abnormalities in neural crest cell migration, while the acquired form results from toxic or autoimmune effects on neurons. It occurs as commonly as Hirschsprung disease and presents most commonly as chronic severe constipation. Diagnosis requires a full-thickness biopsy to see the hypoganglionosis of the myenteric plexus. Treatment is symptomatic.

Intestinal Neuronal Dysplasia

Intestinal neuronal dysplasia is rare compared to Hirschsprung disease. There are 2 types of dysplasia: 1) Type A, which has sympathetic aplasia, myenteric plexus hyperplasia, and colonic inflammation; and 2) Type B, in which the sub-mucosal plexus is affected more, and there is no sympathetic aplasia; this type is indistinguishable clinically from Hirschsprung disease. Type B, however, is benign, and the condition eventually resolves spontaneously. Both type A and type B can be localized or disseminated. Diagnosis for both is made on full-thickness biopsies with findings of hyperganglionosis and giant ganglia.

DISORDERS OF THE EXOCRINE PANCREAS

NOTE

Congenital disorders of the exocrine pancreas are almost always part of a generalized systemic disorder. Essentially, 98% of the pancreatic functional reserve must be lost before pancreatic insufficiency develops.

CYSTIC FIBROSIS

Cystic fibrosis is the most common cause of pancreatic insufficiency in children and is discussed in more detail in the Respiratory Disorders section. Patients who are homozygous for *δ-508* have a very high risk for pancreatic insufficiency.

SHWACHMAN-DIAMOND SYNDROME

Shwachman-Diamond syndrome, an autosomal recessive disorder, is the second most common cause of exocrine pancreatic insufficiency in children. The lesion of the pancreas is acinar cell hypoplasia, with intact function of the pancreatic ducts. Shwachman-Diamond syndrome is also associated with short stature, intermittent or persistent neutropenia, and skeletal abnormalities. Fetal hemoglobin levels are elevated in most patients. About 1/3 of affected boys develop myeloproliferative malignancies. Because of the neutropenia, recurrent infections are common. Pancreatic dysfunction is less severe than that seen in CF, and about 50% have improvement in pancreatic function over time.

RARE CONGENITAL PANCREATIC SYNDROMES

Johanson-Blizzard Syndrome

Johanson-Blizzard syndrome causes pancreatic acinar cell hypoplasia with preserved ductal function. The syndrome presents with agenesis/hypoplasia of the nostrils, cardiac abnormalities, hair anomalies, deafness, hypothyroidism, GU defects, and developmental delay. It does not have bone marrow or skeletal abnormalities.

Pearson Pancreatic and Bone Marrow Syndrome

Pearson pancreatic and bone marrow syndrome is a rare autosomal recessive disease in which patients have pancreatic cell atrophy with fibrosis resulting in depressed acinar and ductal function. Associated hematologic abnormalities include macrocytic anemia with varying degrees of neutropenia and/or thrombocytopenia. Hemosiderosis is common.

Quick Quiz

- What is Shwachman-Diamond syndrome?
- What are the commonly identified etiologies of pancreatitis in children?
- What is Cullen sign? Grey Turner sign?
- Can normal amylase levels occur with acute pancreatitis?
- What radiologic test is usually most helpful in diagnosing pancreatitis?

ACUTE PANCREATITIS

Occurrence / Etiologies

Acute pancreatitis is more common in children than previously thought. Many cases do not have a recognizable etiology but are probably due to an infectious illness. Commonly identified etiologies in children include blunt abdominal trauma (including that due to child abuse), mumps (less commonly seen today, except on Board exams) and other viruses, multisystem disease, various congenital anomalies, and biliary microlithiasis. Other important etiologies to consider include drugs, such as those for HIV (e.g., didanosine or ddI), hemolytic uremic syndrome, Kawasaki syndrome, bone marrow transplant, and head trauma. CF is associated most commonly with chronic pancreatitis, although acute pancreatitis can occur. Alcohol has been increasingly recognized as an etiology in older adolescents.

Clinical Manifestations

Clinically, patients with acute pancreatitis typically present with abdominal pain, persistent vomiting, and fever. The abdominal pain commonly occurs in the midepigastric region and is described as steady and "boring." Children will flex their knees and hips and sit upright or lie on their side. The patient appears very uncomfortable and is irritable. Usually, the abdomen is distended and tender to palpation. During the initial 24–48 hours, the pain increases along with the vomiting. Hospitalization is almost always recommended.

A severe form, acute hemorrhagic pancreatitis, is rare in children. This condition is life-threatening. The child will present acutely ill with vomiting and abdominal pain. Shock and high fever are common. Look on the Board exam for Cullen sign (bluish discoloration around/near the umbilicus) or Grey Turner sign (bluish discoloration of the flanks). In this severe form, the pancreas becomes necrotic and eventually, without therapy, it will be transformed into an inflammatory hemorrhagic mass. The mortality rate is over 50%.

Diagnosis

Diagnosis is difficult and usually is clinical. Serum amylase and lipase are frequently used to aid in the diagnosis; however, normal amylase levels can occur in the setting of acute pancreatitis. Additionally, other disorders can elevate the amylase level, including disorders of the salivary gland (mumps in particular) and disorders that decrease clearance of amylase, as in renal insufficiency. Expect amylase levels to be elevated for 4 days. The isoenzymes can be separated in some centers to differentiate between pancreatic and salivary sources. Lipase will remain elevated for 8–14 days.

You can use plain films of the abdomen to exclude other etiologies. A CXR will exclude pulmonary complications or etiologies. Ultrasound of the abdomen is the easiest and best test, because it can directly visualize the pancreas, making it possible to determine if there are increases in pancreatic size, areas of different pancreatic tissue densities, or dilated ducts, all of which support the diagnosis of acute pancreatitis. Ultrasound also can show gallstones and choledochal cysts and help identify and follow abscesses and pseudocysts of the pancreas (Image 14-16). CT is generally reserved for those cases where ultrasound cannot delineate the anatomy well. See Image 14-17, showing CT scan with arrow at pseudocyst.

Endoscopic retrograde cholangiopancreatography (ERCP) is used for those cases of recurrent pancreatitis,

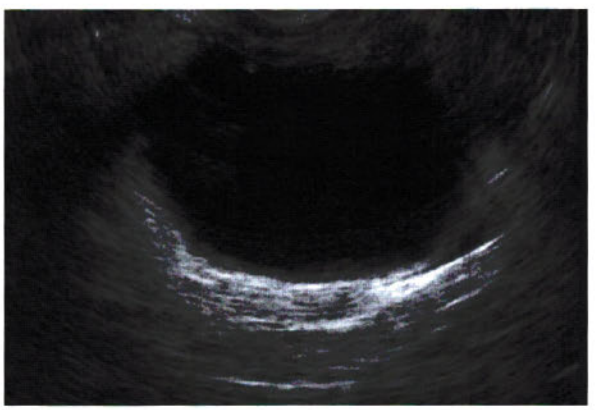


Image 14-16: Ultrasound Showing Pancreatic Pseudocyst

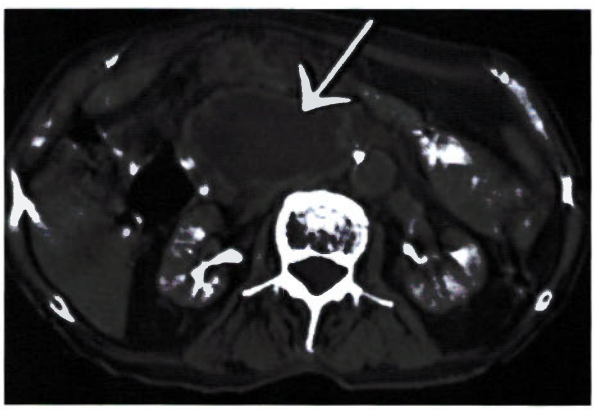


Image 14-17: CT Showing Pancreatic Pseudocyst

pancreas divisum, sphincter of Oddi dysfunction, and disease associated with gallbladder pathology. Additionally, MRI and endoscopic ultrasonography are now available.

Treatment

Aim treatment at relieving pain and returning pancreatic function to normal. In the past, meperidine was used for pain control; however, it is used less often today because of recent reports on the neurologic effects of the drug. Monitor fluids and electrolytes, and replenish as necessary. For those patients who are vomiting, nasogastric suction is helpful. Low-fat feedings are now recommended as soon as the patient is improving and desires to eat. In severe pancreatitis, transpyloric tube feedings with a semi-elemental formula is recommended very early in the course of therapy. Antibiotics are not recommended. Most patients will respond after 2–4 days of therapy. If pancreatic pseudocysts occur, they usually resolve spontaneously. Rarely will they require percutaneous drainage or surgical intervention.

CHRONIC PANCREATITIS

Chronic pancreatitis is rare in children. Most cases are due to hereditary pancreatitis, which is an autosomal dominant disorder with incomplete penetrance. Nearly 80% present before age 20; the mean age of onset is 11 years. Usually, there is a strong family history of pancreatitis. A subset of patients with chronic pancreatitis has a defect in the *PRSS1* gene for a trypsinogen protein that make it hypersensitive to activation. Other defects in pancreatic regulatory proteins, such as the serine protease inhibitor (*SPINK 1* gene), have now also been described. Some unique mutations in the *CFTR* gene have also been identified. Intermittent/repeating episodes of chronic pancreatitis are usually mild to moderate and may resolve over 3–7 days. The frequency and severity of the episodes usually decrease as the child ages. Pancreatic insufficiency can occur in up to 50%, and DM occurs in about 25%. Adenocarcinoma of the pancreas occurs with increased frequency in those affected.

DISEASES OF THE LIVER AND BILIARY TREE

CONGENITAL DISORDERS OF LIVER STRUCTURE

Liver Location Abnormalities

Situs inversus (left-sided) and heterotaxia (central liver) are relatively rare congenital anomalies. Either can occur with other anomalies, such as polysplenia or asplenia syndromes. Many of these patients are without functional difficulties.

Congenital Anomalies of the Portal Vein

Congenital anomalies of the portal vein are frequently associated with cardiac and urinary system abnormalities. Portal vein thrombosis can occur due to umbilical infection; umbilical vein catheterization in the newborn period; pancreatitis; protein C, protein S, and antithrombin III deficiencies; or the presence of anticardiolipin antibodies. You can confirm portal vein abnormalities by Doppler ultrasound, frequently after the patient presents with splenomegaly or esophageal variceal bleeding.

Congenital absence of the portal vein has been described but is very rare.

CONGENITAL ANOMALIES OF THE BILIARY TREE

Choledochal Cysts

Choledochal cysts occur in between 1/13,000 and 1/2,000,000 live births. Asian girls are the most commonly affected group, especially Japanese girls. Nearly 40% present before 1 year of age, and an additional 35% present between the ages of 1 and 6 years. The classically described triad of abdominal pain, jaundice, and palpable right upper quadrant mass occurs in only about 25%. Fever, nausea, vomiting, and pancreatitis are classic symptoms. Use ultrasound to show both intrahepatic and extrahepatic biliary tree dilation. Radionuclide scans can show the cyst with accumulation of tracer. ERCP is useful for determining the anatomy.

There are 5 different types based on anatomic location as classified by Todani. The most common, however, is type I with diffuse enlargement of the common bile duct.

Unfortunately, there is a high incidence of biliary malignancy in patients with choledochal cysts, with rates as high as 17.5% in Japan. Most are adenocarcinomas diagnosed at around age 35 years. Treatment for the cysts is aimed at early removal of the cyst and gallbladder, with reconstructive surgery based on the anatomic location of the cyst.

Structural Anomalies of the Gallbladder

Congenital absence of the gallbladder occurs in about 1/10,000 births and is of little clinical significance if it occurs in isolation. Frequently, though, absence of the gallbladder is associated with extrahepatic biliary atresia, imperforate anus, GU anomalies, bicuspid aortic valve, and cerebral aneurysms.

Hypoplastic gallbladders are more common and occur in about 1/3 of patients with CF. Additionally, hypoplastic malformations occur in trisomy 18. "Double" gallbladder occurs in about 1/10,000.

"Floating" gallbladder occurs in 5% of the population. These gallbladders lack a peritoneal coat and are suspended and pendulous. This makes them more

QuickQuiz

- What are most cases of chronic pancreatitis due to?
- What radiologic modality is useful for diagnosing choledochal cysts?
- What is Caroli disease?
- What is Alagille syndrome?
- What are the cardiac findings associated with Alagille syndrome?

susceptible to torsion, which results in acute, severe RUQ pain with nausea and vomiting.

Extrahepatic Biliary Atresia

Most causes of extrahepatic biliary atresia are acquired, but up to 35% may occur during embryonic development or be fetal abnormalities. These infants present with neonatal cholestatics and absence of bile duct remnants. About 20% have other associated anomalies, including cardiac, GI, or GU systems. Pediatric liver transplantation is lifesaving. Extrahepatic biliary atresia is discussed in greater detail later in this section.

Congenital Hepatic Fibrosis

Congenital hepatic fibrosis is the most common abnormality of the ductal plate, which forms at about 8-weeks gestation and consists of hepatic precursor cells that remodel over fetal life to form the intrahepatic biliary tree. Congenital hepatic fibrosis is usually associated with autosomal recessive polycystic kidney disease. Neonates and infants present with abnormalities of the renal system, and older children and adults present with hepatic manifestations. The ductal plate abnormality results in dilated bile duct structures and portal tracts without interlobular ducts in the center. In children 5–13 years of age, this leads to portal hypertension and presents typically as hematemesis and/or melena due to esophageal varices. The bleeding can be life-threatening and requires endoscopic intervention. On examination, the child will have an enlarged liver, especially the left lobe, and splenomegaly. The liver transaminases are usually normal except for occasional mild elevations. The development of cholangitis is the greatest concern and the prime cause of mortality. Liver biopsy confirms the diagnosis. Treatment can include portosystemic shunting for portal hypertension and antibiotic therapy for cholangitis. Liver transplantation is beneficial for those with chronic cholangitis or progressive hepatic dysfunction. Some with isolated congenital hepatic fibrosis do well and do not require specific therapy.

Caroli Disease

Caroli disease is another abnormality of the ductal plate and is due to a congenital dilation of the larger, segmental intrahepatic bile ducts. If Caroli disease occurs in combination with congenital hepatic fibrosis, it is known as Caroli syndrome. Caroli disease and syndrome are autosomal recessive and present in adolescence or adulthood. Patients present with recurrent cholangitis and abscesses. Liver biopsy can show the hepatic fibrosis, but further diagnosis of Caroli disease requires ultrasound, CT, ERCP, or percutaneous transhepatic cholangiography. These studies will show dilation of the hepatic bile ducts and enlargement of the major intra- and extrahepatic biliary passages. Treat with antibiotics aimed at the cholangitis. If the disease is confined to one lobe, you may consider a partial hepatectomy. Sepsis is a frequent cause of death. Additional complications include cholangiocarcinoma and amyloidosis.

Alagille Syndrome (Arteriohepatic Dysplasia, Watson-Miller Syndrome, Syndromic Duct Paucity)

Alagille syndrome is an autosomal dominant disorder with variable penetrance that is caused by mutations on chromosome 20p in a single gene *JAG 1*, which encodes protein ligands for *NOTCH 1*. It is rare (except on Board examinations), with an incidence of about 1/100,000.

Alagille syndrome is associated with peripheral pulmonary artery stenosis (occasionally tetralogy of Fallot) and neonatal cholestasis. Classically, patients will present with chronic cholestatic liver disease with a "paucity" of small intra-hepatic ducts, "butterfly" vertebrae, abnormal radius/ulna, posterior embryotoxon of the eye (a developmental abnormality marked by a prominent white ring of Schwalbe and iris strands that partially obscure the chamber angle), and characteristic facies. The facies of these children consist of a prominent forehead; moderate hypertelorism; a small, pointed chin; and a saddle or straight nose.

Most patients with Alagille have elevated conjugated bilirubin in the neonatal period. In about 1/2 of patients, hepatobiliary scans fail to show biliary excretion of tracer. Liver biopsy shows reduced numbers of small bile ducts with some giant-cell transformation and cholestasis.

Most patients with Alagille syndrome have a benign course. Cholestasis usually resolves or improves over the first year of life, and most patients do not develop cirrhosis. Some infants have more severe, sometimes progressive, liver disease. Overall mortality approaches 25% and is usually due to cardiac disease, intercurrent infection, or progressive liver disease.

Do not perform Kasai portoenterostomy in infants with Alagille syndrome! Be aware also that children with Alagille are particularly prone to significant intracranial

bleeding with even minor head trauma. This is regardless of their liver function and without a noticeable coagulopathy. Liver transplantation is used only for those with hepatic failure, severe growth failure, and intolerable itching unresponsive to medical therapy.

LIVER TRAUMA

Blunt hepatic injury occurs on a spectrum ranging from a minimal parenchymal hematoma to massive organ disruption. Injuries can result from motor vehicle accidents, falls, bicycle injuries, and child abuse. Suspect blunt hepatic injury in the presence of elevated liver enzymes and conjugated hyperbilirubinemia in a child with a history of trauma or in a suspected child abuse case. However, there is no correlation between the magnitude of the enzyme and bilirubin elevation and the severity of the trauma. The elevated levels usually decrease over 4–6 weeks. CT scan or radionuclide scintigraphy is used initially to identify the extent of trauma, and ultrasound may be used for follow-up exams. Prognosis is determined by the amount and extent of hemorrhage due to vessel injuries. The majority of deaths from blunt trauma to the liver are due to injuries to the posterolateral aspect of the right lobe of the liver, with extension into the hepatic veins.

INFECTIONS OF THE LIVER

Hepatitis A

Hepatitis A is an RNA virus. It is easily transmitted fecal-orally—usually via food or water. It can also be sexually transmitted. There is no transplacental transmission! There are no carrier or persistent states, although occasionally there is prolonged cholestasis (with increased bili and alk phos) for up to 4 months. Incubation period is 15–50 days. (See Figure 14-1, Hepatitis A Serology vs. Weeks after Exposure.)

Diagnosis of acute infection: high titers of anti-HAV IgM in serum (IgG indicates only a previous infection).

Symptoms are unusual in children but very common in adults (70%). Complications are rare—about 1% chance of fulminant hepatitis. Immune globulin (IG) is good prophylaxis only against HAV (use HBIG for hepatitis B). For prophylaxis give either hepatitis A vaccine (see below) or IG in a dose of 0.02 mL/kg as soon as possible, preferably within 2 weeks of exposure. Also give either to all household contacts and sexual or needle-sharing partners, as well as day care and nursing home attendees and staff in close contact with a case. Hepatitis A vaccine is preferred prophylaxis for those ≥ 12 months of age and IG is preferred for those < 12 months of age. Schools, hospitals, or workplace day-to-day contact does not warrant prophylaxis.

An inactivated hepatitis A vaccine (Havrix® and Vaqta®) is available. It is given universally at 1 year of age in 2 doses, 6 months apart. Virtually all those completing the series develop protective levels of antibody to hepatitis A virus (anti-HAV). Trends based on what is now known of the antibody levels suggest protection for up to 20 years in those who complete the series.

Even though the HAV vaccine is universally recommended in the U.S., many people may not have received it as a child. Be on the lookout on the Board exam for these scenarios that indicate a person is at high risk for hepatitis A infection or complications:

- High-risk behavior
- Children > 2 years old living in communities with high rates
- Chronic liver disease
- Travel to high-risk countries
- Patients with hepatitis B or C, because these patients can also have fulminant disease if they get hepatitis A

Hepatitis B

Hepatitis B: Know the 3 main antigenic markers in hepatitis B: (follow along in Figure 14-2).

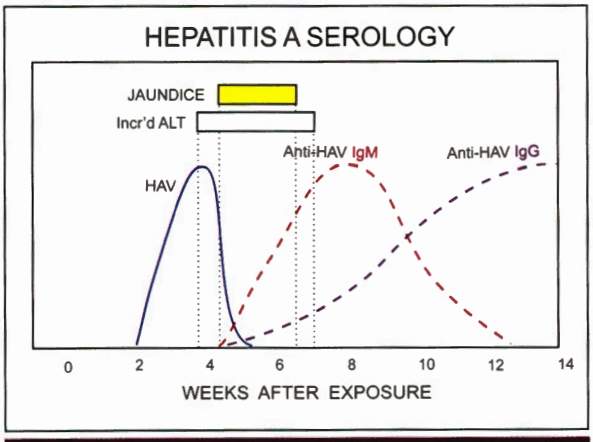


Figure 14-1: Hepatitis A Serology vs. Weeks after Exposure

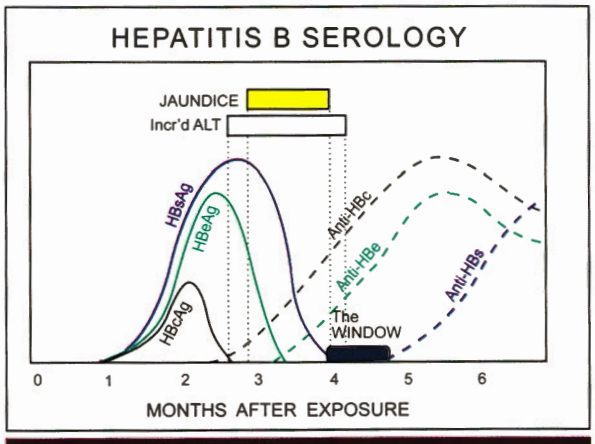


Figure 14-2: Hepatitis B Serology vs. Months after Exposure

QuickQuiz

- How is hepatitis A transmitted from person to person?
- What laboratory test will diagnose acute hepatitis A?
- What can be given to household contacts to prevent spread of hepatitis A once a case has been identified?
- What laboratory test indicates immunity to hepatitis B?
- Which laboratory test implies an increased risk of infectivity for hepatitis B?
- How is hepatitis B transmitted?
- What is the "window period" for hepatitis B infection?
- Hepatitis B is associated with which autoimmune reaction?
- Once infected with acute hepatitis B, who is more likely to develop chronic hepatitis B—an infant or an adolescent?

1) HBsAg. There are 3 HBsAg+ proteins seen in the serum of patients with hepatitis B: One large, double-shelled 42 nm particle that is the intact virion and two smaller 22 nm spherical or rod-shaped protein particles that outnumber the large particle by up to 1,000 to 1! These 22 nm HBsAg+ particles are thought to be just excess viral coat protein. The HBsAg has many different subtypes (adw, adr, etc.). These have no clinical significance, although they are used epidemiologically to evaluate outbreaks. Finding anti-HBs IgG in the serum indicates past exposure to either hepatitis B virion or the vaccine and indicates immunity to the virus.
2) HBcAg. HBcAg+ protein is the core particle (inner shell) of the above 42 nm virion. This protein is retained in the hepatocyte until it is covered with HBsAg+ nucleocapsid outer shell, which will then incorporate the DNA. Free HBcAg+ protein does not circulate in the serum. Antibody to HBcAg appears early in the disease (initially IgM, then IgG) and persists for life, so anti-HBc IgG is the best marker for previous exposure to HBV.
3) HBeAg. HBeAg is a soluble protein made from the same gene as HBcAg; however, unlike HBcAg, HBeAg is secreted from the hepatocytes and circulated in the serum. It correlates with the quantity of intact virus and therefore with infectivity and liver inflammation. The HBe antibody (anti-HBe) appears several weeks after the illness. Detecting HBsAg and HBeAg indicates active virions and high infectivity (more so than HBsAg+ and HBeAg–). The tests for HBeAg and anti-HBe are often not available locally.

Hepatitis B is the only hepatitis virus composed of DNA. Incubation period is 1–6 months. It is transmitted by contaminated serum, blood products, and contaminated needles. Once infected, the first marker detectable in the serum is the antigen, HBsAg. This is followed by the appearance of antibody to the core antigen. After HBsAg becomes undetectable, there is a period of several weeks before the anti-HBs antibody becomes detectable. This is called the "window," and you must measure an anti-HBc IgM during this period to confirm acute hepatitis B.

Hepatitis B is strongly associated with polyarteritis nodosa (PAN). The surface antigen is found in 20–30% of these patients. It appears that the hepatitis B infection precipitates an autoimmune reaction resulting in PAN.

Clinical: First are prodromal constitutional symptoms, which typically resolve at the time jaundice becomes apparent. Occasionally (10–15%), the prodromal symptoms are serum sickness-like, with fever, arthritis, urticaria, and angioedema. This seems to be caused by circulating immune complexes (especially HBsAg+ complexed with anti-HBs) activating the complement system. With the onset of jaundice, the patient usually feels much better but may have liver swelling and tenderness and cholestatic symptoms.

Removal of HBV is T-cell mediated, and the only purpose of anti-HBsAg is to prevent reinfection or initial infection with the use of vaccine.

Hepatitis B immune globulin (HBIG; anti-HBs) provides some protection against hepatitis B, although it appears to only decrease the severity of illness rather than protect the patient from disease. It is effective as prophylaxis and when given in early infection.

The 2 hepatitis B vaccines are composed of HBsAg. They are equally effective, and they are safe for pregnant patients. It is best if the hepatitis B vaccine is given before the patient is exposed to HBV. 95% of immunocompetent patients develop antibodies, whereas only about 50% of dialysis patients do. Because these vaccines are surface antigens, to ensure effectiveness after the course of vaccine has been given, check for anti-HBs—there will be no anti-HBc.

The likelihood of developing chronic HBV is inversely related to age. Chronic HBV occurs in 90% of infants infected at birth, in 25–50% of children age 1–5 years, and in 5% of older children and adults. There is now universal preschool vaccination in the U.S. Overall, less than 1% of patients with hepatitis B develop fulminant hepatitis, but about 5–7% develop chronic carrier states. There are 3 types of carrier states:

1) Asymptomatic
2) Chronic persistent hepatitis
3) Chronic hepatitis B

Table 14-7: Hepatitis B Scenarios

HBsAg	Anti-HBc	Anti-HBs	Interpretation
+	–	–	Acute Infection
+	+	–	3 possibilities: 1) Acute infection (IgM anti-HBc) 2) Chronic Hep B (high ALT, IgG anti-HBc) 3) Inactive carrier (normal enzymes, IgG anti-HBc)
–	–	+	2 possibilities: 1) Remote infection 2) Immunized
–	+	+	Remote infection
–	+	–	3 possibilities: 1) Window disease 2) Remote infection 3) False positive
+	+	+	More than 1 infection. E.g., IV drug user or renal dialysis patient with both acute and chronic hepatitis B (infected with different strains of hepatitis B).

Table 14-8: Types of Viral Hepatitis and Their Serological Tests

	Anti-HAV IgM	Anti-HAV IgG	HBsAg	Anti-HBs IgG	Anti-HBc IgG	Anti-HBc IgM	HBeAg	Anti-HDV
Acute hepatitis A	+	–	–					
Previous HAV	–	+	–					
Acute HBV	–	–	+ early	–	–	+	+	–
Acute HBV—window	–	–	–	–	–	+	–	–
Chronic active HBV	–	–	+	–	+	–	usu +	–
Remote HBV (immune)	–	–	–	+	+	–	–	–
Vaccinated (immune)	–	–	–	+	–	–	–	–
Acute hepatitis D (w/acute HBV)	–	–	+ early	–	–	+	+	+
Acute hepatitis D (w/CAH)	–	–	+	rarely	+	–	usu +	+

The first 2 carrier states are benign. You must do a liver biopsy to differentiate chronic persistent hepatitis from chronic hepatitis B. Chronic hepatitis B is a serious illness—in adults, it often progresses to cirrhosis and is strongly associated with hepatocellular cancer. There have been poor results with liver transplantation so far, and chronic hepatitis B is not considered an indication. There are some treatment protocols with antivirals, interferons, and other agents.

Hepatitis scenarios are listed in Table 14-7 and Table 14-8.

Give the newborn of a mother with hepatitis B HBIG and hepatitis B vaccination. There is a 5–10% transplacental transmission of HBV.

If an asymptomatic patient has HBsAg in the serum, it means either the patient is a carrier or the patient has early hepatitis B—so initial action is only to follow closely (once the patient is infected, neither vaccine nor HBIG helps).

If a person has possible blood exposure to a person with an acute HBV infection and the HBsAg is still negative, the CDC recommends giving that person hepatitis B immune globulin (HBIG), followed by a complete course of HBV vaccinations.

Note: Several months after an episode of hepatitis B, check for loss of HBsAg and HBV-DNA to ensure that it has not become chronic.

Quick Quiz

- In adults, chronic hepatitis B is associated with what 2 serious conditions?
- Prior to 1990, what was the most common cause of transfusion-associated hepatitis?
- Which is more likely to cause chronic hepatitis—hepatitis B or hepatitis C?
- Hepatitis C is associated with which vasculitis?
- Which co-infection does hepatitis D require to cause infection?

Hepatitis C

Hepatitis C is a single-stranded RNA virus. It is now the most common cause of liver disease in the U.S. Hepatitis C has blood-borne transmission and was the cause of 90% of transfusion-associated hepatitis prior to the 1990s. Since then, especially with the 2nd generation anti-HCV assays, the incidence of HCV-related hepatitis has become very rare. The prevalence of HCV infection in children is 0.1–0.2% as compared to 1.8% in adults. Most HCV infections in the U.S. are genotype 1, which happens to be less responsive to treatment.

The following are associated with an increased risk of hepatitis C:

- IV drug abusers
- Prisoners
- High-risk sexual behavior: STDs, prostitutes, > 5 sexual partners a year
- Blood transfusion before 1990
- Tattoos and body piercing
- Snorting cocaine

Whereas only 1% of adults with hepatitis B develop chronic disease, 70–80% of acute HCV infections become chronic! Hepatitis B has high virus counts, whereas hepatitis C has low virus counts.

These low virus counts are consistent with the more insidious nature of hepatitis C:

- Only 25% of acute infections are symptomatic.
- HCV infection has an increased likelihood to become chronic.
- The chronic form is relatively benign (25% are only carriers, 50% have no symptoms but have abnormal LFTs, 25% have chronic active disease with symptoms).

It is also consistent with the low rates of sexual transmission seen in monogamous couples: only 5% after 10–20 years. This is low but does occur, so recommend safe sex. Sexual transmission increases with multiple sexual partners.

Needle-stick transmission from a known infected patient is about 5–10%.

Transplacental infection is < 5%.

Extrahepatic disease includes small vessel vasculitis with glomerulonephritis and neuropathy, mixed cryoglobulinemia, and porphyria cutanea tarda (PCT) (Image 14-18). Mixed cryoglobulinemia presents as a small vessel (leukocytoclastic) vasculitis with a rash consisting of "palpable purpura" or "crops of purple papules."

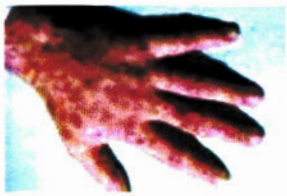


Image 14-18: PCT

70–80% of patients infected with HCV develop chronic hepatitis—and about 25% of these get end-stage cirrhosis after 20–25 years! And 1–4% of patients with cirrhosis develop hepatoma each year. Chronic HCV infection has become the #1 cause of adult liver transplants in the U.S. It must be assumed that many of these were infected during childhood.

There is no vaccine for hepatitis C, although it appears there will be one in a few years.

Lab tests:

- Within 2–4 months after an episode of hepatitis C, recheck for loss of HCV-RNA (PCR) to ensure that it has not become chronic.
- In a person positive for anti-HCV, confirm positive antibodies with the RIBA (recombinant immunoblot assay) test (to exclude false-positive test). If the RIBA is positive, check for active virus by ordering an HCV-RNA viral load. This is necessary because the anti-HCV does not confer immunity (as does the HBV antibody).

Protocols for treatment are interferons and ribavirin, although the response rate is at best nearing 50%.

Mixed cryoglobulinemia can result from chronic hepatitis B or C (in addition to various other occult viral, bacterial, and fungal infections).

Hepatitis D

Hepatitis D is an RNA virus that requires a coexistent hepatitis B virus infection for the hepatitis D to become pathogenic. It is usually found in IV drug abusers and high-risk HBsAg carriers. It typically does not make an acute HBV infection much worse, but, if acquired as a superinfection in an HBV carrier, the infection is frequently very severe. If acquired acutely, HDV does not increase the risk of chronic hepatitis B. Immunity to hepatitis B implies immunity to hepatitis D. Diagnosis: Anti-HDV IgM.

Hepatitis E

Hepatitis E, a single-stranded RNA virus, spreads fecally and orally the way HAV does. Found in the Far East, Africa, and Central America, it frequently is due to contamination of water supplies after monsoon flooding. Recently, anti-HEV has been demonstrated in pigs in Midwestern U.S. states and in rats in Maryland, Hawaii, and Louisiana. Like hepatitis A, it has no known chronic form. Unlike hepatitis A, hepatitis E carries a very high risk for fulminant hepatitis in the 3rd trimester of pregnancy—with a 20% fatality rate. With acute hepatitis and negative serology in a traveler, think of hepatitis E.

Hepatitis G

Hepatitis G is blood-borne, like hepatitis B and C. Mode of transmission is not well defined but is similar to HCV. There is evidence of infection in 1.5% of blood donors. It causes < 0.5% of community-acquired hepatitis. There is no evidence that HGV causes chronic liver disease.

See Table 14-8 for a review of the serologic tests done with hepatitis A, B, and D.

Epstein-Barr Virus

Epstein-Barr virus (EBV) is a DNA virus that is transmitted by close person-to-person contact with infected secretions, most commonly saliva. Liver involvement is common in EBV infection and presents with hepatosplenomegaly, mild-to-moderate elevation of transaminases, and occasional jaundice. The liver disease tends to be mild and transient but can be severe and long lasting, particularly in those who are immunocompromised. A small number of patients can have fulminate liver failure. Findings of EBV as an etiology for severe disease include a liver biopsy (rarely needed) showing portal and lobular inflammation with sinusoidal infiltration of mononuclear cells. Some recommend short courses of prednisone to help alleviate the liver dysfunction if it is severe. Antiviral agents are not helpful in the treatment of EBV infection of the liver. The normal course, however, is to document infection by blood testing and allow the disease to resolve on its own.

Cytomegalovirus (CMV)

CMV infection of the liver can be quite severe in the neonate and resembles idiopathic neonatal hepatitis. You can see classic cytoplasmic inclusions in the biliary epithelium and hepatocytes in only 5% of those affected, but these are virtually pathognomonic when they are found. CMV can eventually lead to cirrhosis in some neonates.

Other Viruses

Parvovirus B19 rarely causes liver involvement, but recent case reports have implicated it as an etiology for fulminant liver failure, especially in infants. Mumps and measles (para-myxoviruses) can occasionally cause liver damage.

Final scenario on viruses and the liver: You are presented on the Boards with a patient who has evidence of acute hepatitis. What screening serologic tests do you order to determine if hepatitis A, B, or C is involved?

Answer: For hepatitis A, IgM HAV; for hepatitis B, HBsAg (hepatitis B surface antigen) and IgM HBc (IgM antibody to hepatis B core); and for hepatitis C, anti-HCV antibody.

METABOLIC LIVER DISEASES

Note

Galactosemia, fructose intolerance, glycogen storage diseases, hereditary tyrosinemia, and disorders of fatty acid oxidation are discussed in the Metabolic Disorders section.

Gilbert Syndrome

Gilbert syndrome occurs in 2–10% of the population. It is a benign genetic disorder that is due to an alteration in the promoter for the bilirubin uridine diphosphate glucuronyltransferase (UDP-GT) gene. This change in the promoter leads to a less active, and relative deficiency of, UDP-GT. This results in a mild, indirect hyperbilirubinemia, usually below 5 mg/dL, if liver functions are measured for some reason. There is no associated hemolysis or hepatocellular damage. It becomes apparent most times during episodes of stress or fasting, when the patients become mildly jaundiced. No treatment is required, and no morbidity or mortality is associated with it.

Crigler-Najjar Syndrome Type I

Crigler-Najjar syndrome type I is more severe than type II (see below) and is due to a complete absence of bilirubin UDP-GT activity. It presents in the newborn period with severe indirect hyperbilirubinemia and requires phototherapy and/or exchange transfusions. There is no conjugated bilirubin. Kernicterus is a major concern. DNA testing can confirm the diagnosis post- and prenatally. Mainstay of therapy is phototherapy, although this is difficult to maintain long term. Liver transplant can be curative.

Crigler-Najjar Syndrome Type II

Crigler-Najjar syndrome type II results in partial activity of bilirubin UDP-GT. Hyperbilirubinemia of < 10 mg/dL is usual. It resolves with phenobarbital and other inducers of cytochrome P450, but phenobarbital is not recommended for long-term therapy due to its neurodevelopmental complications from long-term use. It does not require specific therapy and is not associated with increased morbidity or mortality.

Quick Quiz

- How is hepatitis E transmitted?
- Which female patient should you be most concerned about if she gets hepatitis E?
- Can EBV cause significant liver disease?
- What is Gilbert syndrome?
- How does Crigler-Najjar syndrome type I differ from Crigler-Najjar syndrome type II?
- What is Dubin-Johnson syndrome?
- What drug is associated with Reye syndrome?
- How does α_1-antitrypsin deficiency present?
- What are the eye findings in Wilson disease?

Dubin-Johnson Syndrome

Dubin-Johnson syndrome is due to a deficiency in the *cMOAT/MRP2* gene, which encodes the canalicular transporter of conjugated bilirubin. It presents with mild conjugated hyperbilirubinemia of 3–8 mg/dL. There is no hepatocellular injury associated. Urine coproporphyrins show mainly isoform I. It does not require specific therapy and is not associated with increased morbidity or mortality.

Reye Syndrome

The incidence of Reye syndrome peaked in the 1960s and 1970s and is very rare today. Reye syndrome is an acute liver disease with hyperammonemic encephalopathy. It appeared to be associated with aspirin use in children with an intercurrent viral infection, such as influenza or chickenpox. Vomiting is a common presenting finding, and, soon after emesis, AST/ALT values rise. Jaundice is not a specific finding of this disorder, but an elevated PT is common. Elevated ammonia is usual. The prognosis is determined by the neurologic rather than hepatic findings, the latter of which frequently resolve over several days. Treat by correcting metabolic abnormalities and minimizing intracranial hypertension.

α_1-Antitrypsin Deficiency

α_1-antitrypsin deficiency can cause progressive liver disease and occurs with an incidence of 1/2,000 live births. Suspect this diagnosis in any child with chronic liver disease. To diagnose, measure α-antitrypsin concentration and phenotype the α_1-antitrypsin protein. The liver disease can present as neonatal jaundice, juvenile cirrhosis, chronic hepatitis, or hepatocellular cancer. Cholestatic jaundice occurs in 10–15% of infants who are homozygous for the deficiency, and nearly 50% of infants who are homozygous will have abnormal liver tests. Giant-cell hepatitis is the classic histologic finding in neonates. Periodic acid-Schiff-positive staining of the liver is classic also, showing that hepatocytes containing the ab-normal protein α_1-antitrypsin deficiency are associated with emphysema in young adults.

Most infants with neonatal liver disease will improve by 4 months of age for reasons that are unclear. A majority will remain healthy throughout childhood. A few will present later in life with cirrhosis or hepatocellular carcinoma. If patients progress to liver failure, liver transplant is curative.

Wilson Disease

Wilson disease is an autosomal recessive disorder of copper metabolism that occurs with an incidence of about 1/100,000 to 1/500,000 births. The disease results from the excessive accumulation of copper in the eyes, liver, kidneys, and brain. This results in degenerative changes in the brain and liver and formation of Kayser-Fleischer rings in the cornea (Image 14-19). The gene is mapped to chromosome 13.

The disease begins with accumulation of copper in the liver. The clinical presentation varies widely. Most children do not present before the age of 5, and those who present in childhood usually do so with hepatic manifestations, including hepatomegaly and/or acute hepatitis. Hepatic insufficiency occurs later. Fulminant hepatitis is rare before adolescence.

Adolescents and adults may present with mostly neurologic and psychiatric dysfunction. These can include falling grades in school, behavioral changes, tremors, and slurred speech. If left untreated, dysarthria and dystonia eventually develop.

The Kayser-Fleischer rings are frequently absent in children who have only hepatic disease. These are copper deposits in the inner lining of the Descemet membrane and are almost always found in those with neurologic symptoms.

Image 14-19: Wilson Disease, Kayser-Fleischer Rings

Suspect this disorder in children and adolescents with unexplained acute or chronic liver disease, neurologic symptoms of unexplained origin, acute hemolysis, psychiatric illness, behavioral change, Fanconi syndrome, or unexplained bone disease.

Know all of the following (!): The best screening test is the serum ceruloplasmin level, but remember it is not diagnostic. Most patients with Wilson disease will have low ceruloplasmin levels. Early in the disease, serum copper levels may be high, and 24-hour urinary copper excretion is increased, sometimes to 1,000 μg/day (normal urinary copper excretion is < 40 μg/day). If you are still uncertain about the diagnosis, you can give a dose of D-penicillamine, which will increase urinary excretion of copper to nearly 2,000 μg/day in those with Wilson disease. Liver biopsy is the gold standard for diagnosis and will show markedly elevated hepatic copper content.

Screen family members of those with proven cases. This usually includes checking a serum ceruloplasmin and 24-hour urinary copper excretion. If abnormal, conduct liver biopsy.

Treat with copper-chelating agents, which lead to the rapid excretion of excess copper. The most common agent used is oral penicillamine in a dose of 1 g/day in 2 doses before meals for those older than 10 and 0.5–0.75 g/day for those younger than 10. With therapy, hepatic and neurologic function will improve, and Kayser-Fleischer rings will disappear. If the patient cannot tolerate penicillamine, try triethylene tetramine dihydrochloride. Limit oral intake of copper to less than 1 mg/day. Have patients avoid foods such as liver, shellfish, nuts, and chocolate. If the copper content of the water is elevated, suggest a demineralizer.

Treatment is lifesaving; in fact, those without treatment will die. For those patients who already have fulminant liver failure or decompensated cirrhosis, liver transplant is indicated. Some recommend liver transplant for those with progressive neurologic disease, but this indication is controversial. In screened siblings who are asymptomatic with the disease, implement penicillamine therapy.

Hemochromatosis

Hemochromatosis is the excessive storage of iron, mainly in the form of hemosiderin in parenchymal cells. It can result in abnormalities in the function and structure of the liver, heart, pancreas, gonads, skin, and joints. There are 3 forms of this disease:

1) Hereditary hemochromatosis
2) Neonatal hemochromatosis
3) Transfusion-induced hemosiderosis

Hereditary hemochromatosis is most commonly due to a mutation in the *HFE* gene, but it is variably expressed. This is not a disorder of childhood, but children can have elevated iron studies. Adults develop cirrhosis, bronzing of the skin, and DM. If families are screened, you can prevent disease by periodic phlebotomy; for children, this is usually not necessary until adolescence.

Neonatal hemochromatosis is an acquired syndrome due to severe liver damage at some period before delivery. Mortality is > 90%. These children present with cholestatic jaundice with coagulopathy and/or ascites at birth. Some advocate the use of antioxidant cocktail as therapy in these infants.

Finally, transfusion-induced hemosiderosis occurs in those patients who repeatedly receive red cell transfusions. It most commonly occurs in those with congenital or acquired anemias who require frequent transfusions. Monitor iron overload and treat with chelation therapy.

Progressive Familial Intrahepatic Cholestasis (PFIC)

Progressive familial intrahepatic cholestasis refers to a group of inherited disorders in which bile is not formed properly. PFIC1 (formerly known as Byler disease) and PFIC2 are characterized by normal serum GGT (γ-glutamyl transpeptidase) but with severe cholestasis. PFIC3 has elevated serum GGT levels.

PFIC1 usually presents between 3 and 6 months of age with conjugated hyperbilirubinemia and severe, unremitting pruritus—but remember: GGT is normal! It is due to a mutation in the *FIC1* gene on chromosome 18. Fat-soluble vitamin deficiencies are common, including rickets and vitamin K deficiency. These children have persistent diarrhea with fat malabsorption and protein loss. Poor growth is common. Cirrhosis develops in early childhood and requires liver transplants. Even after liver transplant, bouts of pancreatitis and diarrhea are common.

PFIC2 differs from PFIC1 in that the gene mutation is *SPGP* and occurs on chromosome 2. These children do not have pancreatitis or diarrhea, but they have prominent liver disease with normal GGT. It is most commonly seen in Middle Eastern Europeans.

PFIC3 differs from the other two progressive familial intrahepatic cholestasis diseases in that the cholestasis is associated with an elevated GGT. Jaundice is usually less prominent, but the pruritus is still severe. Patients with PFIC3 present later and have a slowly progressive disease process.

DRUG-INDUCED HEPATOTOXICITY

Drug-induced hepatotoxicity in children is relatively uncommon, but the subject occurs with some regularity on Board exams in relation to specific drugs.

Acetaminophen is a predictable hepatotoxin and is the most common cause of liver failure in the United

QuickQuiz

- How may you diagnose Wilson disease?
- What is the most common etiology for hereditary hemochromatosis?
- How does PFIC1 present?
- What is necessary to replenish glutathione stores in patients taking acetaminophen?
- How do you diagnose autoimmune hepatitis?
- What is primary sclerosing cholangitis associated with?

Kingdom. Its toxicity is dose-dependent and due to shunting down a minor pathway that produces a toxic metabolite when the glucuronidation pathway is depleted. N-acetylcysteine replenishes glutathione stores and allows the liver to metabolize acetaminophen without generating toxic metabolites. There are nomograms you can utilize to determine the risk of hepatotoxicity based on the time since ingestion and measured metabolite level. In severe toxicity, emergent liver transplant may be required.

Idiosyncratic hepatotoxic reactions have been reported with many drugs, but a few are noted with greater frequency. These include phenytoin, sulfasalazine, and halothane. Various antibiotics, including erythromycin and trimethoprim/sulfamethoxazole, can cause hepatic injury.

Oral contraceptives are associated with hepatic vein thrombosis (Budd-Chiari syndrome) and liver adenomas. Use of androgens by adolescent athletes to enhance performance is also associated with liver toxicity.

Except for acetaminophen overdose, no specific therapy is useful for most liver toxicities. Usually, supportive care and stopping the offending agent are the only means to potentially reverse the course.

AUTOIMMUNE HEPATOBILIARY DISEASE

Autoimmune Hepatitis

Autoimmune hepatitis refers to a variety of distinct diseases that affect the liver and frequently overlap with disorders that affect the bile ducts and other hepatic elements. The etiology of autoimmune hepatitis is unknown, but it appears to have genetic features. It is likely that a viral infection or drug exposure may initiate the disorder in those susceptible.

There are really 3 types of autoimmune hepatitis:

1) Type I is known as the "classic" form and affects females > males between the ages of 10 and 20 years, and also between 45 and 70 years. It is associated with the presence of smooth muscle antibodies and/or antinuclear antibodies (ANA).
2) Type II occurs in younger children (males = females) and is characterized by liver-kidney microsomal-1 antibody (anti-LKM-1). These children present with more severe liver disease than those in Type I.
3) Type III occurs in adults primarily and is characterized by anti-soluble liver antigen (anti-SLA).

Clinically, any of these 3 types can present in various ways. Most commonly, patients initially will have only malaise, weight loss, and/or anorexia. Serious complications may not present until cirrhosis and portal hypertension have already occurred, and the child/adolescent presents with variceal bleeding. Jaundice can be quite variable. Always look for a family history of other autoimmune diseases, such as thyroiditis, arthritis, and inflammatory bowel disease.

Diagnosis depends on finding the serum antibody markers in the face of elevated aminotransferases with an elevated total protein due to hypergammaglobulinemia. Always exclude viral hepatitis, especially hepatitis C, which can have elevated ANA or LKM antibodies. Usually, you must conduct a biopsy to show portal lymphoplasmacytic infiltrates that can extend to the surrounding hepatic lobule.

Initial treatment is immunosuppression with corticosteroids. Other agents used include azathioprine, cyclosporine, and tacrolimus. Liver transplant may be useful in refractory cases, but autoimmune hepatitis can recur in the transplanted liver.

Primary Sclerosing Cholangitis

Primary sclerosing cholangitis is characterized by chronic fibrosing inflammation of the intra- and extrahepatic bile duct and has unknown etiology. Secondary sclerosing cholangitis has the same findings but is due to choledocholithiasis, postoperative stricture, toxin-induced bile duct injury, AIDS, or Langerhans-cell histiocytosis. Primary sclerosing cholangitis is associated with inflammatory bowel disease and occasionally is ANCA-positive, both of which indicate a possible immunological etiology.

Clinically, patients present variably. Neonates may have jaundice and present as though they have biliary atresia. Older children can be asymptomatic or have fatigue, hepatosplenomegaly, or abdominal discomfort with itching. For some children, cirrhosis and portal hypertension may be the first clues. Always consider primary sclerosing cholangitis in any child with inflammatory bowel disease if there is evidence of hepatobiliary dysfunction.

Laboratory will usually show elevated alkaline phosphatase and GGT. Low titers of anti-SM or anti-LKM antibodies may be present. On histologic examination, the classic "onion-skin lesion" is pathognomonic but not

common. The best test to confirm the diagnosis is endoscopic retrograde cholangiography, which will show alternating normal, strictured, and dilated portions of the biliary tree, known as "beading."

No specific therapy is beneficial. Treat with supportive care, fat-soluble vitamin supplements, and anti-itching agents. Some recommend using ursodeoxycholic acid to stimulate bile flow. Recommend liver transplant if cirrhosis and portal hypertension have occurred.

IDIOPATHIC NEONATAL (GIANT-CELL) HEPATITIS

Idiopathic neonatal hepatitis is a catchall phrase for newborns with liver damage where infectious and metabolic etiologies have been ruled out. The liver disease presents histologically as multinucleated giant cells and can occur in 40% of infants with cholestasis. Jaundice usually occurs in the first week after birth but can take 1–3 months to appear. Acholic (clay-colored or gray) stools and dark urine are common. Hepatomegaly is universal; splenomegaly occurs in 50%. Laboratory testing shows an elevated alkaline phosphatase with an elevated bilirubin of about 8–12 mg/dL, of which over 50% is conjugated. Albumin and GGT are usually normal.

Diagnosis relies on excluding other etiologies and finding giant-cell transformation around the central veins on liver biopsy.

Except for supportive care and fat-soluble vitamin supplementation, no specific therapy is helpful. 70–80% will have a complete recovery by 6–8 months. Those who don't improve will likely develop cirrhosis and portal hypertension.

AAGENAES SYNDROME

Aagenaes syndrome is very rare (except on exams). It is an autosomal recessive disorder of Norwegian families. It presents as severe cholestasis in Norwegian newborns. Lymphedema of the lower extremities is a characteristic finding. Histologically, it resembles giant-cell neonatal hepatitis (see above). Children gradually improve without specific therapy.

EXTRAHEPATIC BILIARY ATRESIA

Extrahepatic biliary atresia is not common, yet it is the most common reason for pediatric liver transplantation in the United States. The specific etiology is unknown, but many believe it to be acquired from infection, metabolic disorder, or environmental agents. Biliary atresia results from one of these or other insults leading to destruction of bile ducts, progressing from extra- to intrahepatic, then leading to fibrosis, biliary cirrhosis, and eventual liver failure.

Clinically, cholestatic jaundice usually appears during the 2nd or 3rd week of life but can occur at birth. Look for clay-colored (acholic) stools and dark urine as clues to biliary atresia. Hepatomegaly is common at diagnosis. Most jaundiced infants will have hyperbilirubinemia (both conjugated and unconjugated), elevated alkaline phosphatase, GGT, and transaminases. The gallbladder is frequently not seen on ultrasound. Radionuclide scans will show failure to excrete radioisotope. Conduct liver biopsy and cholangiogram if studies do not rule out the diagnosis.

These children need to be identified as soon as possible. The surgical drainage procedure is more successful the earlier the lesion is discovered. Treat initially with the Kasai procedure, a bile-drainage procedure making a hepatoportoenterostomy. In this procedure, a loop of the intestine is attached to the porta hepatis. This allows bile flow from the liver. Typically, it must be done before 3 months of age. A successful Kasai procedure can avoid or delay the need for liver transplantation. Prognosis varies. In those where bile flow is not reestablished and jaundice never resolves, hepatic failure ensues, usually before 1 year of age. In a large majority, bile flow is reestablished and jaundice slowly resolves over several months, but cirrhosis develops over time. Liver transplantation is required for both of these outcomes. Only a small minority achieve apparent permanent drainage post-Kasai without progression of the disease in the liver itself. Once the Kasai is done, these children are at risk for ascending cholangitis and must be followed carefully for signs of fever and worsening jaundice.

CHOLELITHIASIS

Cholelithiasis (gallstones) in healthy children and infants is likely more common than previously thought. Most are asymptomatic and are incidental findings on radiological studies. These should just be followed. Classic symptoms include right upper quadrant pain, vomiting, and jaundice. Pain can occur with or without meals and may resolve once the stone has passed.

Certain children are predisposed to developing stones, including those children with hemolytic disease (particularly sickle cell), those on chronic TPN, those with short bowel syndrome, and adolescent pregnant females. The most common complication in children with cholelithiasis is pancreatitis due to an obstructing stone or stones.

Plain x-rays can reveal stones with high calcium content, but most require ultrasound. A majority of pediatric gallstones are pigment stones and will not respond to oral bile acid therapy. If stones are picked up incidentally, many pediatricians recommend observation only. In those with biliary colic, cholangitis, cholecystitis, or pancreatitis, removal is recommended.

QuickQuiz

- What is the best radiologic test to confirm primary sclerosing cholangitis?
- What is Aagenaes syndrome?
- What procedure is useful as early therapy for extrahepatic biliary atresia?
- Which children are more likely to develop gallstones?
- Under what conditions is hydrops of the gallbladder found?
- What is the most common malignant liver tumor of childhood? Which laboratory test will be elevated?

CHOLECYSTITIS

Cholecystitis is inflammation of the gallbladder; it can occur with or without stones (acalculous cholecystitis), although it rarely occurs in children at all. Right upper quadrant pain and tenderness on palpation of the gallbladder are common. If the pain worsens with inspiration, this is known as Murphy sign. Other things can cause similar pain, including hepatitis, hepatic abscess, Fitz-Hugh-Curtis syndrome (gonococcal perihepatitis), pancreatitis, appendicitis, pneumonia, pyelonephritis, and renal stones. Most patients will have an elevated WBC count with a left shift and mild increases in bilirubin and transaminases. Amylase is frequently elevated even in the absence of pancreatitis. Markedly elevated bilirubin, alkaline phosphatase, and/or GGT levels indicate obstruction of the biliary tree with a stone. Ultrasound is best to visualize stones or a thickened gallbladder. Hepatobiliary scan can demonstrate poor or no visualization in the presence of an inflamed gallbladder. Children have a 30% complication rate, which includes perforation, abscess, and empyema. Most recommend hospital admission with intravenous fluids and gut rest. Antibiotics are not recommended routinely, unless the patient has worsening fever or tenderness. Perform cholecystectomy for cholecystitis with stones.

Acalculous cholecystitis can be acute (< 1 month duration) or chronic. It presents acutely, similarly to calculous cholecystitis, except there are obviously no visible stones. It occurs most commonly after a life-threatening illness, burn, or trauma. The chronic form is also known as biliary dyskinesia.

HYDROPS OF THE GALLBLADDER

Hydrops of the gallbladder refers to an acute noncalculous, noninflammatory enlargement of the gallbladder. It is associated with Kawasaki syndrome, streptococcal pharyngitis, prolonged fasting, TPN, and Henoch-Schönlein purpura. Patients complain of RUQ pain with a palpable mass. Fever, vomiting, and jaundice are common. Ultrasound shows a markedly dilated, stone-free gallbladder. Acute hydrops rarely requires cholecystectomy. If performed, a laparotomy will show a large, edematous gallbladder that contains white, yellow, or green bile. Usually, treating the underlying condition will result in the gallbladder returning to normal over several weeks.

TUMORS OF THE LIVER AND BILIARY TREE

Tumors of the hepatobiliary system are rare in children, comprising about 1–4% of all solid tumors. If they occur, they are most common in the right lobe of the liver. In children, benign tumors are much more frequent than malignant ones. The common benign tumors include hemangiomas, adenomas, focal nodular hyperplasia, and mesenchymal hamartomas.

Hepatoblastomas are the most common malignant liver tumors in children. They are single masses found in infancy. The serum α-fetoprotein level is markedly elevated in these children and is useful for diagnosis and monitoring after therapy (for recurrence). With complete resection and postoperative chemotherapy, survival rates approach 50%. Liver transplant has been used successfully in cases where complete resection cannot be done.

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